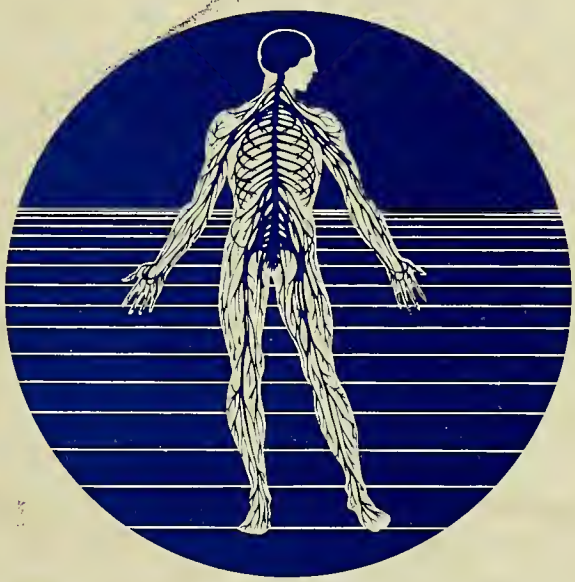
National Institute of Neurological and Communicative Disorders and Stroke

Annual Report



Fiscal Year 1983

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

ANNUAL REPORT

October 1, 1982 through September 30, 1983
National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

ASSOCIATE DIRECTOR FOR BRANCHES: Dr. Irwin J. Kopin

---

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

ANNUAL REPORT
October 1, 1982 through September 30, 1983
National Institute of Neurological and Communicative Disorders and Stroke

Alphabetical Listing of NINCDS Principal Investigators

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

ANNUAL REPORT
October 1, 1982 through September 30, 1983
National Institute of Neurological and Communicative Disorders and Stroke

INTRAMURAL RESEARCH PROJECTS
Numerical Inventory

Intramural Research Projects - Numerical Inventory (Cont'd)

Intramural Research Projects - Numerical Inventory (Cont'd)

NEW INITIATIVES FOR FY 1983

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

ANNUAL REPORT

October 1, 1982 through September 30, 1983

Office of the Director

National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

Annual Report of the Director
National Institute of Neurological and
Communicative Disorders and Stroke
October 1, 1982 through September 30, 1983

Fiscal Year 1983 was characterized by important changes in the senior leadership of the Institute, a continuing increase in the scope and impact of administrative problems, significant advances in scientific productivity intramurally and extramurally, and clearer identification of research opportunities for understanding the functioning of the human nervous system and preventing the disability and morbidity associated with the neurological and communicative disorders.

Senior Leadership

In Fiscal Year 1983, appointments were made for the leadership positions of Institute Director, Institute Deputy Director and Director of the Institute's Intramural Research Program. This completed the recruitment of the Institute's executive management team. All appointees are experienced NIH science managers and able to assume responsibility rapidly for the conduct of Institute affairs. Thus, the thrust of the recent decade of initiative will be continued and perhaps accelerated. In the latter quarter of this fiscal year, the Director of the extramural Demyelinating, Atrophic and Dementing Disorders Program was reassigned by the PHS Commissioned Corps to another position and it is anticipated that a replacement will be appointed by the beginning of calendar year 1984.

In regard to the leadership and management of the Institute's direct operations (management, intramural research, contract research), personnel continues to be the Institute's major strength and simultaneously its severest problem. To recruit and maintain a superior staff are the aspirations of which dreams are made. The scientific excellence of the working environment and its high degree of productivity are assets; the cumbersome and counter-productive regulations governing public servants in a research environment are the deficits. For example: Salary scales for established persons of scientific excellence are not competitive with the market place--even in competition with other Government health agencies which have special scales; managerial rating and reporting procedures that may be useful in regulatory agencies have adapted poorly to the issues of the biomedical scientist and his/her supporting staff. Despite these, the excellence of the NINCDS scientific and leadership staff continues, although staff morale is an ever increasing and now a major problem.

Organizational Issues

Most of the major issues of the organizational structure of the Institute have been resolved. Organizational units have been established in the intramural and extramural programs that represent the major thrusts of both Institute responsibility and opportunity. There are several areas of research opportunity that require added organizational emphasis (e.g., transplantation; regeneration; gene modification; orphan drug development) but resource limitations restrict necessary organizational development.

In addition, the search for a Chief of the intramural Clinical Communicative Disorders Branch (otolaryngology; audiometry; speech pathology) has continued for two years with disappointing results. Clinical scientists of NINCDS quality find the Federal pay scale too low; those who would consider coming do not meet our scientific standards of excellence. The Institute can no longer reserve the resources set aside for this program and thus the search will have to be discontinued and the resources reassigned. Since a national focal point for clinical research and training in the communicative disorders would meet a national need, this recruitment failure has been a disappointment but the few active clinical investigators of quality in this area are clearly not available at this time for Federal employment.

Scientific Issues

A member of Congress recently asked: "Is this the decade of the neurosciences?" I believe the answer is yes. Having completed the scientific assignment of describing the gross and microscopic anatomy of the nervous system and its electrophysiological functioning, neuroscientists have now turned to understanding its molecular structure and cellular function. The nervous system has become the target of the so called "new biology," capturing the attention of the scientific community. Examples of the anticipated product of this research include the localization on the genome of the genetic foci for neurological function and dysfunction, an understanding of the microenvironment controlling the trophism of neural cells, insight into the programmed death of nerve cells, and a clear understanding of the character and balance of neurotransmitters that prescribe neural function. As a result, we can anticipate new clinical insights and strategies for clinical intervention in enzyme deficiency neurological disorders, in immunological disorders of the nervous system, in demyelinating and atrophic neurological disorders and in the important vascular and traumatic disorders of the nervous system. In the several areas of the communicative sciences and disorders, a small cadre of skilled scientists are now addressing the fundamentals and the pathology of central processing, reinforcing and adding to the knowledge about end organ sensory and motor phenomena.

In summary, the NINCDS continues to meet its obligations and responsibilities as a premier science and science administration organization. Its staff is well trained and highly productive. It is responsive to national needs and scientific opportunity. As Director, I am proud of it, of its accomplishments and of its quality. I look forward to the next year, anticipating even greater accomplishment.

ANNUAL REPORT
October 1, 1982 through September 30, 1983
Equal Employment Opportunity Office
Office of the Director
National Institute of Neurological and
Communicative Disorders and Stroke

INTRODUCTION

Public Law 92-261, the Equal Employment Opportunity Act of 1972, requires that all Federal personnel actions be free from discrimination and that affirmative action programs be developed to carry out the purpose and intent of the Public Law. In 1978, Congress passed the Civil Service Reform Act stating that "it is the policy of the United States to provide the people of the United States with a competent, honest and productive Federal work force reflective of the Nation's diversity."

Beginning in 1969, the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) embarked on a course of action to insure equality of opportunity for all its employees in recruitment, selection, and promotion. During the past five years the Institute has initiated special programs to help expand the pool of ethnic minorities and women in biomedical research, especially the neurological and communicative sciences.

ORGANIZATION AND MANAGEMENT

The National Institute of Neurological and Communicative Disorders and Stroke's affirmative action, and civil rights programs are centered in the Institute's 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 contracts and grants, coordinating the implementation of Executive Order 12320, "Historically Black Colleges and Universities," providing leadership for the overall effectiveness of the Institute's Federal Equal Opportunity Recruitment Program, 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 programs to help increase the pool of minorities, women, and the handicapped in biomedical research, particularly the neurosciences.

The Institute has an EEO Advisory Committee that provides advice to the Director, NINCDS, on matters relating to Equal Employment Opportunity in the Institute, 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 NIH Handicapped Employees Advisory Committee.

HIGHLIGHTS OF ACCOMPLISHMENTS IN FY'83

FEDERAL EQUAL OPPORTUNITY RECRUITMENT PROGRAM

The Federal Equal Opportunity Recruitment Program (FEORP) is a component of the Civil Service Reform Act. It requires each Federal agency to conduct a continuing program for the recruitment and placement of minorities and women in various job categories in the Federal work force. In FY'81, the NIH selected nine occupations for FEORP targeted recruitment. They were:

Biologist	Secretary	Microbiologist
Chemist	General Administrative	Nurse
Medical Officer	Health Scientist Administrator	Contract Specialist

In FY'83, eleven employees (ten females and one minority) were selected for positions in NINCDS under this program. Under the Health Scientist Administrator series, Dr. Katherine L. Bick was appointed Deputy Director of the NINCDS.

SUMMER PROGRAMS

THE NIH SUMMER RESEARCH FELLOWSHIP PROGRAM

This highly selective program is designed to provide research training to medical students that are pursuing a career in research or academic medicine. In FY'83, five minority students from medical schools throughout the country (Vanderbilt, Georgetown, Howard, University of Virginia, and Albert Einstein) were selected for training positions in the Institute's research laboratories.

The Graduate Program

This competitive program provides exposure to biomedical research for college graduates and medical students. In FY'83, 29 students were selected for positions in this program. Ten (or 34%) were minorities and 11 (or 38%) were non-minority females.

The Undergraduate Program

This program is designed to provide on-the-job training and research experience for undergraduate students contemplating a career in research or medicine. In FY'83, 14 students were selected for sub-professional positions in this program. Four (or 29%) were minorities and four (or 29%) were non-minority females

Summer Externship Program

This program provides exposure to research methodology for third-year medical students participating in the Summer Externship Program of Provident Hospital in Baltimore. Students spend four weeks at the NIH and four weeks at Provident Hospital. Eight students from Meharry Medical College were selected for the program in Fiscal Year 1983.

Committee on Institutional Cooperation (CIC) Minorities Fellowship Program in the Sciences

The CIC (a consortium consisting of the "Big Ten" universities*, and the University of Chicago) Minorities Fellowship Program in the Sciences is designed to increase the representation of ethnic minorities in the sciences at the Ph.D. level. Rosabel R. Garcia, a participant in this program from the University of Chicago, was selected for a summer position in the Preclinical Pharmacology Section.

Visiting Students

Two female students were appointed to summer research training positions in the Institute in FY'83 as guest workers. They were:

Deborah Price, Surgical Neurology Branch, Sponsor: College of Medicine and Dentistry of New Jersey, New Jersey Medical School

Joanna Calne, Developmental and Metabolic Neurology Branch, Sponsor: Tay-Sachs Foundation

GRADUATES OF THE SUMMER PROGRAMS PURSUING CAREERS IN THE NEUROSCIENCES

The Summer Programs in NINCDS are designed to provide research training and experience for college students planning a career in academic medicine or biomedical research. Through these programs, the NINCDS encourages academically talented students, especially minorities and women, to pursue biomedical research careers in the neurosciences.

The Results

Two minority students are pursuing a career in neurosurgery and research (Duke University School of Medicine and Johns Hopkins University School of Medicine).

Four minority students are pursuing a research career in the neurosciences and academic medicine through the combined M.D.-Ph.D. Program (Johns Hopkins University School of Medicine, Stanford University School of Medicine, and Albert Einstein College of Medicine).

Two minority students are pursuing a Ph.D. in the neurosciences (Washington University, and the University of Chicago).

A participant in the Summer Research Fellowship Program is planning a career in neurology with an emphasis on research.

PROMOTIONS AND AWARDS

Promotions

In Fiscal Year 1983, 17 employees were awarded promotions in the Institute. Seven (or 41%) were minorities and 16 (or 94%) were females.

Awards

Twenty-nine employees received recognition (cash and within-grade increases) under the Federal Incentive Awards Program in FY'83. Approximately six (or 21%) were minorities and 23 (or 79%) were women.

EXCEPTIONAL SUMMER EMPLOYEE AWARD

Nine students received the NINCDS Exceptional Summer Employee Award in recognition of their exceptional performance in the NINCDS 1983 Summer Program. Five (or 56%) were minorities and four (or 44%) were females.

TRAVEL FELLOWSHIPS FOR MINORITY NEUROSCIENTISTS

The NINCDS in Fiscal Year 1982, 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. A major goal of the Program is to attract minority students to careers in the field of neuroscience and provide encouragement in the early stages of such career development. Fourteen fellows were selected for the program in FY'83.

SEMINARS AT ACADEMIC INSTITUTIONS AND SCIENTIFIC MEETINGS

Academic Institutions

The Institute's EEO Officer and other staff members conducted seminars for students at several academic institutions to discuss research training programs and career opportunities at the NINCDS. In FY'83, seminars were conducted at the following academic institutions:

Yale University School of Medicine, New Haven, Connecticut
Howard University College of Medicine, Washington, DC
Atlanta University Center, Atlanta, Georgia
Meharry Medical School, Nashville, Tennessee
Morehouse School of Medicine, Atlanta, Georgia
Fisk University, Nashville, Tennessee
Harvard University, Boston, Massachusetts
Johns Hopkins University School of Medicine, Baltimore, Maryland
University of Minnesota, Minneapolis, Minnesota
University of Massachusetts at Amherst
City College of the City University of New York
Hunter College, New York
Washington University School of Medicine, St. Louis, Missouri

High Schools (Washington Metropolitan Area)

Eastern High School, Washington, DC
McKinley High School, Washington, DC
Shaw Junior High School, Washington, DC
Regina High School, Hyattsville, Maryland

SCHEDULED SCIENTIFIC MEETINGS

The Minority Biomedical Research Support Symposium, April 7-9, 1983
The Student National Medical Association, April 1, 1983
The Society for Neuroscience Annual Meeting, November 3, 1983
The National Institute of Science Meeting, March 25, 1983

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

Through cooperative agreements with the National Institute of General Medical Sciences and the Division of Research Resources, the NINCDS supports components of the MBRS and MARC programs that relate to the overall mission of the Institute.

In FY'83, the Institute awarded $136,991 to support MBRS grants at the University of New Mexico, City College of New York, and San Jose State University.

A MARC undergraduate student (Morehouse College) was selected for a summer research training position in the Neuroimmunology Branch.

SUPPORT TO HISTORICALLY BLACK INSTITUTIONS (HBIs)

Executive Order 12320, "Historically Black Colleges and Universities", requires Federal agencies to review their programs, eliminate barriers, and develop new initiatives to increase the participation of historically Black colleges and universities in Federally sponsored programs.

Some activities in support of the Executive Order by NINCDS in Fiscal Year 1983 were:

Three research grants were awarded to two historically Black colleges (Howard University College of Medicine and Meharry Medical College).

Six students from HBIs were selected for positions in the NINCDS Summer Program.

Two neuroscientists from HBIs were awarded fellowships under the Travel Fellowships for Minority Neuroscientists Program.

COMMUNITY OUTREACH

To help increase the participation of minorities, women, and the handicapped in the biomedical sciences, particularly the neurosciences, the Institute's EEO Officer conducted a series of seminars and laboratory tours at the NIH for science students from the following schools, community organizations, and scientific meetings:

The Pre Health Club of Benedict College;
The Minority High School Student Research Apprentice Program at the University of Maryland School of Medicine;
The United Negro College Fund Premedical Summer Institute at Fisk University;
The Rappahannock Region Upward Bound Program at Mary Washington College;
The MBRS Symposium;
The Summer Health Science Academy at Howard University College of Medicine;
The Upward Bound Program for Science Students at the University of Maryland;
The Summer Academic Advancement Program of the North Carolina Health Manpower Development Program; and
The Center for Advanced Training in Cell and Molecular Biology at Catholic University.

EEO ADVISORY COMMITTEE

Some activities of the Committee this past fiscal year were:

The Committee submitted a comprehensive report to the Director concerning affirmative action and personnel issues in the Institute (training, awards, promotions); and

Coordinated the Annual NINCDS All Employees' Meeting.

Program Staff

Levon Parker	EEO Officer
Monretta Cooper	EEO Specialist
Willermarie Johnson	Secretary
James Pomeroy	EEO Counselor
Selena Abrams	Chairperson, EEO Advisory Committee
Thelma Martin	NIH Women's Advisory Committee
David Kerr	NIH Handicapped Employees Advisory Committee

---

*University of Chicago
University of Illinois at Urbana-Champaign
University of Illinois at Chicago
Indiana University-Bloomington
Indiana University-Indianapolis
University of Iowa
University of Michigan
Michigan State University
University of Minnesota
Northwestern University
Ohio State University
Purdue University
University of Wisconsin-Madison
University of Wisconsin-Milwaukee

ANNUAL REPORT
October 1, 1982 through September 30, 1983

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

Sylvia W. Shaffer, Chief

Within the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS), dissemination of research information to the public is chiefly the responsibility of the Office of Scientific and Health Reports (OSHR). This Office advises the NINCDS Director and the executive staff on ways to inform a variety of public audiences of the results of research conducted and supported by the Institute. Tasks of this Office range from simply mailing a pamphlet in response to an inquiry, to writing news stories about NINCDS research activities, to writing and coordinating technical state-of-the-art research reports.

For OSHR, Fiscal Year (FY) 1983 was a time of extensive reorganization and staff changes. The retirements of four long-time OSHR employees and the departure of several other employees left the office seriously understaffed for most of the year.

Mrs. Margaret Suter and Mrs. Edith Messitte both retired from the Public Inquiries (now Public Liaison) Section, the latter after 31 years' service with NIH, 27 of them with OSHR. Mrs. Agnes Reday, a valued editorial assistant in the Scientific Publications Section, retired after 21 years of Government service. Mrs. Laura Brodsky retired from her position as chief secretary for the office in December 1982, and her replacement, Mrs. Linda Davis, left in August 1983 to return to employment in the private sector. Mr. Raymond Fleming was promoted to chief of the Scientific Publications Section, replacing Mr. Robert Hinkel who retired in FY 1982. Ms. Diane Striar transferred from the Public Liaison Section to fill the writing/editing position in the Scientific Publications Section that Mr. Fleming vacated on his promotion. Ms. Striar's former position in the Public Liaison Section remained unfilled throughout the year because of lack of qualified candidates.

Despite the hardships these shortages caused, the vacancies offered the OSHR chief a good opportunity to reorganize and redistribute duties for greater efficiency. Expansion of word-processing capability within the Office also made possible redistribution of duties.

As structured at the end of FY 1983, the OSHR is divided into two Sections: 1) Public Liaison (formerly Public Inquiries), under the direction of the OSHR deputy director, Mrs. Lynn Trible. This Section has now assumed responsibility for liaison with voluntary and professional societies (duties formerly assigned to staff members of the Scientific Publications Section), and for reporting on NINCDS extramural research activities. The Section retains responsibility for public inquiries, distribution of publications, and exhibits. The deputy chief brings to the Section responsibility for media liaison, and will now be able to delegate some of these duties to other Section staff members.

2) Scientific Publications Section, under the direction of Ray Fleming. This Section retains responsibility for production of all NINCDS publications, and has new responsibilities for reporting on intramural research.

As this year marked the end of a Department-wide moratorium on publishing, the OSHR undertook a crash effort to catch up on postponed projects and to begin new projects with the goal of maintaining the approved publication schedule. While these efforts were constrained by a dollar ceiling imposed on all NIH publishing, the greater limitation was the lack of staff to handle increased production. By the end of the fiscal year, staff problems were close to being resolved, promising greater productivity in FY 1984.

A major undertaking this year was OSHR support of the NINCDS-sponsored international symposium on research issues in positron emission tomography (PET), held at NIH in June 1983. OSHR staff was involved in the organization of this symposium: preparation of program, flyers, announcements, and other materials; publicity; and subsequent preparation of proceedings. A free-lance science writer was given a contract to report on the symposium, and the resulting article made a two-part, front-page story for the NIH RECORD. In related initiatives, a contract was awarded to a science writer for a pamphlet on PET research and for an overview article on the NINCDS brain-imaging program. Both pieces were completed in FY 1983 and will be published in FY 1984.

OSHR also helped organize and publicize the first annual Marjorie Guthrie Lecture in Genetics, in cooperation with the National Institute of General Medical Sciences information office. Publication of this first lecture (by Dr. David Baltimore) is a carry-over project to be completed in FY 1984.

OSHR liaison with voluntary health agencies concerned with neurological and communicative disorders continued to be strong in FY 1983. OSHR staff participated in a two-day meeting of voluntary health agency representatives held at NIH in the spring, and continued providing agencies with RESEARCH CURRENTS--a compilation of NINCDS news stories and publications. Throughout the year, OSHR staff members advised voluntary agency representatives on publications, how to run a science writers' seminar, how to reach the media with a research story, and other public information concerns. Assignment of the important voluntary liaison function to the Public Liaison Section should considerably strengthen OSHR service to this important public in FY 1984.

A major OSHR objective this year was to increase public understanding of the NINCDS role in Alzheimer's disease research. Primary materials for this undertaking were the NINCDS pamphlets, "The Dementias: Hope Through Research" and "Alzheimer's Disease: A Scientific Guide for Health Care Practitioners." Both publications were widely distributed throughout the year, particularly after Ann Landers mentioned the NINCDS pamphlet on the dementias in her nationally syndicated newspaper column. Considerable media interest was generated as a result of an OSHR story on new findings about the cholinergic system in Alzheimer's disease. A major feature story on this research, written for OSHR by a free-lance science writer and based on a presentation at the NANCDS Council, was published in the NIH RECORD and picked up and widely distributed through NIH NEWS & FEATURES and NIH HEALTHLINE. NINCDS scientists were prominently featured in a two-page

article on Alzheimer's disease published in TIME magazine, and OSHR arranged for the NINCDS deputy director to appear on the nationally televised Merv Griffin Show to discuss this growing national health problem.

In FY 1983, the OSHR again responded to Congressional calls for reports of research progress in specified areas--the so-called "Moyer" reports. Because the nervous system is involved in so many disorders, OSHR has become responsible for preparing or contributing to the greater number of Moyer reports of any NIH office. This year OSHR took the lead in preparing reports on stroke, spinal cord injury, multiple sclerosis, and Huntington's disease research, and contributed to seven other reports being prepared by other NIH units. OSHR also prepared the NINCDS submission for the NIH International Activities Report.

Public Liaison (Public Inquiries) Section

In FY 1983, the Public Liaison Section lost all three of its professional writing/editing staff members. One writer transferred in November to another position within OSHR, and attempts to fill that vacancy quickly were not successful. That position was still vacant in August when two long-time section staff members, including the Section chief, announced their retirement plans. Responsibility for public inquiries was assumed by the remaining professional staff members in OSHR. Plans for a Section reorganization had been drawn up earlier and were immediately put into effect, with one new writer in place by the end of the fiscal year and recruitment for the remaining two positions under way.

A major result of the reorganization was the consolidation within this Section of responsibility for all written and telephone inquiries--duties formerly distributed throughout OSHR. The clerk/typist position was upgraded to include responsibility for processing incoming mail, preparing responses in final form, and handling all incoming telephone calls from the public. Two word-processing units are in place, and equipment has been ordered to permit the Section to become fully automated in FY 1984.

This year, 840 individually prepared responses were sent to the Institute's lay and medical audiences. Another 144 responses were written in answer to controlled letters from the Congress and White House. A total of 132,291 publications were mailed in response to requests for information on specific disorders. Unusual media interest in shingles and in the dementias resulted in an avalanche of requests for "Hope Through Research" pamphlets on these conditions. More than 20,000 copies of "Shingles--Hope Through Research" were distributed in response to public requests generated by a mention of the pamphlet in Modern Maturity. Ann Lander's column on Alzheimer's disease brought the Institute more than 15,000 requests for copies of "The Dementias--Hope Through Research." These mass mailings were accomplished by contracting a portion of the distribution through the sheltered workshop at St. Elizabeth's Hospital in Washington, D.C.

Most frequently requested of the remaining publications distributed this year were those on Alzheimer's disease (6,075), hearing loss (5,350), chronic pain (4,698), aphasia (4,648), epilepsy (4,355), brain tumors (3,865), cerebral palsy (3,520), stroke (3,290), Parkinson's disease (3,120), multiple sclerosis (2,880), stuttering (2,848), dizziness

(2,385), headache (2,225), Huntington's disease (2,230), and amyotrophic lateral sclerosis (2,195). The balance of the requests were distributed among 55 other NINCDS publications.

In addition, 41,900 publications were sent out to fill bulk requests from voluntary health agencies, medical centers, and local and state agencies. An estimated 7,000 publications were distributed to scientists at medical meetings.

The Public Liaison Section is charged with managing the Institute's exhibits program, and this year coordinated with NIH Medical Arts to produce a special exhibit to support the Demyelinating, Atrophic, and Dementing Disorders Program at the national meeting of the American Veterinary Association. The purpose was to interest AVA members in applying for NINCDS support of research to identify animal disorders that model human neurological diseases. The visuals and copy used in the exhibit--both provided by the Public Liaison Section--dramatized the goal of the program, and attracted many visitors to the NINCDS booth. The picture panels for this exhibit are also appropriate for display at a number of other meetings.

This year a message board panel was added to the exhibit system. The panel, which can be easily joined to any of the NINCDS exhibits, is overlaid with a special writing surface where information of special interest to meeting attendees can be recorded. The new accessory has proved particularly useful to NINCDS scientists, who can post on the panel the hours they will be at the booth to confer with grantees.

In the fall of 1982, the NINCDS exhibit was shown at meetings of the XII Symposium Neuroradiologicum in Washington, D.C.; the American Academy of Otolaryngology in New Orleans; the Society for Neuroscience in Minneapolis; and the American Hearing, Speech, and Language Association in Toronto. From January through September 1983, the exhibit was sent to meetings of the Association of Research on Otolaryngology in St. Petersburg; the American Association of Neurosurgeons and the Epilepsy International Fifteenth Symposium, both in Washington, D.C.; the Triological Association in New Orleans; and the American Academy of Neurology in San Diego. In cooperation with the NINCDS Equal Employment Opportunity Office, OSHR also sent exhibits to meetings of the Minority Biomedical Symposium and the National Black Association for Speech, Hearing and Language, both in Washington, D.C., and to the National Medical Association in Chicago.

The initial training of a Stride Program employee who was recently assigned to OSHR is being performed in the Public Liaison Section.

Scientific Publications Section

The Scientific Publications Section produces and distributes publications for the general public and a variety of professional and scientific audiences. The Section serves various administrative units of the Institute, ad hoc committees preparing reports, and outside organizations in the neurological and communicative disorders fields. The services include planning, clearing, budgeting, writing, pretesting, editing, and obtaining photographs for publications; securing and overseeing design, layout, and printing; initial distribution and storage of publications; and subsequent revision and reprinting.

The Section also produces feature-length and shorter news stories. These stories appear in NINCDS NOTES, a monthly Institute news service to journal editors; RESEARCH CURRENTS, a triannual packet of lay-language science articles sent to many voluntary health agencies; and other NIH information vehicles such as the NIH RECORD, NEWS & FEATURES, and SEARCH FOR HEALTH.

Although the beginning of FY 1983 marked the demise of the Department-wide moratorium on printing, strict Departmental controls on publication development remained in effect. In spite of these controls, the Section succeeded in obtaining clearance for all of NINCDS's 14 publication proposals--including a 4-color Guide to Positron Emission Tomography to be published early in FY 1984.

A priority project of the 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 various neurological and communicative disorders. During this fiscal year, new pamphlets on Parkinson's disease and stroke were sent to the printer; well under way at the close of FY 1983 were pamphlets on head injury, headache, amyotrophic lateral sclerosis, and dizziness. This heavy schedule was designed to make up for production losses that occurred during the FY 1982 Federal printing moratorium. The Section also reprinted 50,000 copies of The Dementias: Hope Through Research in anticipation of a demand created by an Ann Landers's column on this subject.

NINCDS fact sheets meet the public need for information about rare and little-known neurological and communicative disorders. This year, the Section reprinted the Institute's autism fact sheet and revised fact sheets on Tourette syndrome and neurofibromatosis.

Among the annual publications produced for NINCDS by the Section were the voluntary health agency directory, the NANCDS Council directory, and the directory of professional societies. In addition two fact books were produced: the July 1982 version which had been held up by Departmental clearance delays, and the regularly scheduled September 1983 edition.

The Section was also heavily involved in assisting various NINCDS program areas to meet their publication needs. Staff members helped to produce four large publications for the Laboratory of Central Nervous System Studies: bibliographies on Creutzfeldt-Jakob disease, hemorrhagic fever with renal syndrome, and ALS/Parkinson-Dementia of Guam, and an account of Dr. Carleton Gajdusek's South Pacific expedition. For the Office of Biometry and Field Studies, the Section assisted in reprinting the National Survey of Stroke and in producing a flyer for the stroke data bank workshop. Section personnel were also involved in developing for that office a consistent design for a future "family" of survey brochures.

Other publications in which the Section was substantially involved were the proceedings of the human brain dissection workshop, for the NINCDS scientific director; the annual report of the Convulsive, Developmental, and Neuromuscular Disorders Program; and reprints of articles for the Communicative Disorders Program and Intramural Research Program.

During FY 1983, approximately 57 articles were written for NINCDS NOTES, and 6 short news stories appeared in the NIH RECORD. Longer feature stories were produced for the NIH RECORD, NEWS & FEATURES, and other NIH information vehicles on the following topics: otitis media, Alzheimer's disease, multiple sclerosis, Gaucher's disease, PET, and a new test for genital herpes.

The Section's continuing interactions with both Federal and private agencies promised to increase the effectiveness of OSHR programs. Active liaison was maintained with the Federal Publisher's Committee, an interagency organization concerned with the high cost and marketing restrictions that apply to Government publications. Consultation was held with the information staff of the National Heart, Lung, and Blood Institute concerning their computerized publications record system which the Section hopes to implement for NINCDS in FY 1984. The Section also counseled two outside organizations--Personal Health Information Services of Boulder, Colorado, and the Alberta (Canada) Senior Citizens Bureau--about reprinting NINCDS pamphlets on chronic pain and the dementias.

Media Liaison

This year OSHR media liaison activities focused on providing national high-impact media with information about NINCDS research in high-priority research fields: Alzheimer's disease, stroke and trauma, spinal cord injury, hearing loss, and brain imaging.

Major national attention was won for the NINCDS brain-imaging program with the successful placement of a front-page story about NINCDS PET research in the nationally distributed USA TODAY, and with placement of the NINCDS director as a guest on the nationally televised Merv Griffin Show to discuss PET research. Numerous other stories appeared in local and professional media as a result of OSHR's efforts to promote the international conference on PET research held at NIH in June 1983. Since media interest in PET research and brain imaging remains high, OSHR concentrated this year on building effective working relationships with the staff of the Clinical Center Nuclear Medicine Department, ensuring their cooperation for filming in the PET laboratory.

OSHR arranged for the Institute director to make a second guest appearance on the Merv Griffin Show to discuss research on spinal cord injury. There was an exceptionally good public response to this appearance, with numerous letters and telephone calls received both at Merv Griffin Productions and at NINCDS. The Institute director used this opportunity to inform the public about highly promising results in nervous system regeneration achieved by Dr. Lloyd Guth, NINCDS grantee at the University of Maryland in Baltimore.

In the third appearance by an NINCDS staff member on the Merv Griffin Show, the NINCDS Deputy Director discussed Alzheimer's disease as part of an OSHR initiative to draw national attention to the Institute's important work in this area.

In her role as media liaison specialist, the OSHR deputy chief oversaw the production and distribution of press releases to national and professional

media announcing the appointment of the Institute's new director, deputy director, and scientific director. Interviews were arranged between the Institute director and top management and leading science writers of major national media outlets such as TIME, Inc., WALL STREET JOURNAL, and NEW YORK TIMES, and with U.S. NEWS & WORLD REPORT for its 50th anniversary issue. Opportunities were also arranged for the Institute director to speak about spinal cord injury research with the SAN FRANCISCO EXAMINER and on a variety of topics with many other prominent newspapers and magazines.

Considerable media interest was expressed in the results of an NINCDS-supported study of the effectiveness of antidecongestants as a treatment for otitis media in children. OSHR prepared a press release on the controversial findings of this study, and responded to media and public inquiries for interviews and further information.

Throughout the year, numerous media inquiries were handled every day on topics encompassing the full range of NINCDS research. OSHR has established an excellent reputation for prompt, reliable response to media inquiries and is more and more frequently sought out as an information resource by reporters working on brain research stories.

OSHR was also helpful this year in encouraging a young minority student, who had completed a summer writing/editing internship in OSHR, to apply for an internship offered by a local television station. After an array of interviews, the student won the coveted internship and is showing considerable talent for television news. OSHR continues to work with this student to develop story ideas based on NINCDS research which are then offered to the television station for staff consideration. Topics suggested to date include intensive monitoring of epilepsy, shingles, and PET research.

ANNUAL REPORT
October 1, 1982 through September 30, 1983
Office of Planning and Analysis
Office of the Director

National Institute of Neurological and Communicative Disorders and Stroke

The Office of Planning and Analysis (OPA) is organizationally comprised of an Office of the Chief, the Management Information and Data Section (MIDS) and the Analysis and Reports Section (ARS). 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 including prevention, nutrition, technology assessments and other trans-NIH research areas such as digestive diseases, dermatology and arthritis.

OPA also administered the Institute information and data system. This has required that MIDS collect, classify, organize, store and retrieve data on research and research training grants/awards, contracts, and intramural research projects. Auxiliary files (e.g., history, award rate, and Council data) have been maintained to supplement the NIH IMPAC records. That Section became the focal point for automatic data processing (ADP) activities in the Institute and, as such, was responsible for their reporting to PHS, DHHS, and GSA, e.g., the annual ADP Plan and related Institute equipment inventories/utilization.

MIDS responded to approximately 350 requests for data on the Institute's extramural and intramural program activities. The information was used for NINCDS program/budget planning, program evaluation, and in response to requests from both within and outside NIH (e.g., the NINCDS and NIH Director and staff offices, other Federal agencies, voluntary and professional associations, and Congress). Examples of such output included material for meetings of the NINCDS-sponsored Stroke Center Directors and the Institute's National Advisory Council, estimates of funding levels for that Council, and data on trends of approval and funding rates for 1977-1982.

Several types of recurring reports were prepared for the use of Institute staff. These included the printed Fiscal Year Summary Book Series (four volumes) containing a wide-range of information on NINCDS research and training grant/award activities. Twelve computerized quarterly data reports on currently active program activities, as well as contracts, were

prepared and distributed. Additionally, twenty other reports were developed and disseminated for the purpose of keeping NINCDS informed about grants to be considered by its Council. The Research and Training Data Books, another set of publications, were discontinued during the year based on agreement within the Institute's extramural programs that such data exist elsewhere. The FY 1983 data book is expected to be expanded to reflect additional areas of Institute reporting.

Other recurrent activities within ARS included development of an annual evaluation plan for the research programs of the Institute as well as the development and coordination of an annual research plan. The latter plan, for the first time, stressed areas of scientific opportunity. Its development required close contact and coordination, both within the Office of the Director and with key staff throughout NINCDS.

ARS also coordinated the development of the Institute Annual Report. It provided an overview of the total scope of NINCDS research as to science, program, and budget. Summaries of programs, contracts and intramural research projects were included. The Section provided technical assistance to program areas in order to ensure uniformity of format and editorial quality.

OPA coordinated activities relating to the development and review of the annual NINCDS Implementation Plan. The plan required setting funding priorities within the text of program objectives, research opportunities, and available resources. This was done in close collaboration with other components of the Office of the Director, NINCDS. In addition, the OPA collected data and produced an inventory of NINCDS clinical trials activities. This inventory will be updated on a regular basis.

On June 16 and 17, in Bethesda, Maryland, NINCDS sponsored a special conference on "Research Issues in Positron Emission Tomography." Conferees from Canada, Europe and other nations (as well as from various medical centers throughout the United States) were in attendance. Both prior to and during this international symposium, OPA contributed a substantial portion of the logistical support required to achieve the successful outcome experienced by those in attendance.

Response was provided to a large number of ad hoc queries from a variety of private and public sources regarding NINCDS research as it relates, for example, to NHLBI, NIEHS, pain research, research on the handicapped, toxicology, aging, and several other important areas. Where necessary, financial projections were developed by the Budget Office in collaboration with OPA.

As the legislative focus for the Institute, OPA continued to work with appropriate staff of NIH/OD to monitor legislative developments in order to strengthen and maintain all elements of the Institute's mission. Legislative proposals pertaining to NIH reauthorization and other areas of vital interest to NINCDS were reviewed and recommendations forwarded to the Institute Director. OPA developed testimony for his appearances before key committees of the Congress.

In reviewing the myriad of activities undertaken by the OPA in FY 1983, two stand out as being of critical importance. They are the development and implementation of an expanded system for NINCDS program data coding and retrieval and the development and conduct of a Senate mandated study of research opportunities and needs of the NINCDS.

Implementation began in July of an expanded system for NINCDS program data coding and retrieval. Fiscal year 1984 data will be coded using the enhanced system. Earlier in the year, an OPA Working Group reexamined the data needs of the Institute on its grants/awards, contracts, and intramural research projects, with particular emphasis on the data requirements of the Office of the Director, NINCDS. The Working Group considered overall coding structure alternatives, determined the necessary number and types of fields, and developed the appropriate terms/codes for each field. The effort led to the issuance of a comprehensive coding manual consisting of field codes, applicable coding rules, term definitions, and an alphabetical glossary of terms in the hierarchies for reference purposes. Data continuity with the prior coding structure was provided through conversion tables and numerous cross-references throughout the document. The overall development and implementation effort provided the following additional data enhancements:

1. Increased comprehensiveness and specificity of coding and retrieval term hierarchy with flexibility for expansion that greatly improves the scope and relevance of retrieved data, reducing dependence on DRG's CRISP data, and reducing subsequent manual effort.

2. Additional pertinent aspects of a project are now coded to maximize data availability and reduce previously existing inflated/deflated dollar amounts in some reporting.

3. Percentage breakdowns provide more accurate data and avoid manual effort for basic-applied-development research activities, special interest areas, disease or disorder, and scientific field.

4. Data on basic/applied/development research and special interest areas (trans-NIH activities, prevention, age, population, etc.), were automated to more effectively meet NIH and Department information needs and eliminate the extensive manual effort previously required.

Finally, in its report on the FY 1983 Appropriation for the Department of Health and Human Services, the Committee on Appropriations of the Senate of the United States stated: "Because of the opportunities available in research on the nervous system, the Committee finds it necessary to have an evaluation completed by a nongovernmental agency of the research opportunities and research needs of the NINCDS." The OPA developed the contract and an award was made in June. In August, the Contractor (Tracor Jitco, Inc.) convened a panel of 25 experts in the basic and clinical neurological and communicative sciences. Recommendations were made in a variety of scientific and fiscal areas of critical interest to NINCDS. It is anticipated that following clearance by the DHHS, copies of the final report will be publicly available early in FY 1984.

CONTRACT NARRATIVE

Office of Planning and Analysis
Office of the Director
National Institute of Neurological and Communicative Disorders and Stroke

Fiscal Year 1983

Contractor: Tracor Jitco, Inc., Rockville, Maryland (NO1-NS-3-2347)

Title: An Evaluation of Research Opportunities and Needs of the NINCDS in the Neurological and Communicative Sciences

Date Contract Initiated: June 6, 1983

Contractor's Project Director: Thomas Sexton, Ph.D.

Current Annual Level: $100,997

Objectives: This contract was awarded at the direction of the Committee on Appropriations of the Senate of the United States. In its report on the FY 1983 Appropriation for DHHS, the Committee stated: "Because of the opportunities available in research on the nervous system, the Committee finds it necessary to have an evaluation completed by a nongovernmental agency of the research opportunities and research needs of the NINCDS."

Major Findings: In August, 1983, the Contractor convened a panel of 25 experts in the basic and clinical neurological and communicative sciences. The panel made recommendations as to which areas of research provide opportunities to produce advances in both the understanding and the treatment of the many diseases that affect the nervous system. Recommendations were also made as to resources needed to realize these goals.

Significance to the Program of the Institute: If we are to properly take advantage of the research opportunities confronting us in the basic and clinical neurological and communicative sciences, priorities must be discussed and decisions regarding allocation of resources must be made. The Contractor's report will be reviewed by DHHS and submitted to the Congress.

Proposed Course: The contract will expire on October 12, 1983.

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

ANNUAL REPORT
October 1, 1982 through September 30, 1983

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)

PROJECT REPORTS

Table of Contents (cont'd)

Table of Contents (cont'd)

Table of Contents (cont'd)

Annual Report
for period October 1, 1982 through September 30, 1983
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 advance the mission of NINCDS in the areas of neurology and communicative disorders. The scientists in OBFS use the methods not only of biostatistics and computer science, but also of demography, epidemiology, survey design and physics in a number of program areas, such as computerized clinical data banks, national surveys of disease, and clinical trials.

OBFS is responsible for implementing and managing two collaborative, longitudinal projects, the Stroke and Traumatic Coma Data Banks. The pilot data bank studies have demonstrated that the process leading to the development of high quality research data offers a formidable challenge, but is achievable. The data banks represent a mechanism which offers a logical, scientific and disciplined approach to the aquisition of needed, high quality, focused research data. To a very considerable extent, the OBFS data bank mechanism resembles that of a good clinical trial, where the discipline and the constraints are routinely recognized to be of critical importance to a successful product.

The Stroke Data Bank provides a structure to study hospitalized stroke patients at four academic hospital centers. In the Pilot Stroke Data Bank, subarachnoid hemorrhage patients had the highest rate of complication, lacunar infarct patients the lowest. About 40% of patients with a complication experienced more than one. Overall, about 30% of hospitalized stroke patients had one or more complications.

A study of lacunar infarctions presented at the American Neurological Association Meeting described clinical features, laboratory findings and outcomes of lacunar infarction cases. One hundred of 1158 patients in the data bank had lacunar infarcts. One-third of these showed some improvement during the initial 24 hour period from onset. Lacune was the type of infarction most often associated with history of hypertension or diabetes and had the best functional prognosis and least mortality of all stroke types.

Part of the pilot phase of the project, a study of stroke incidence in a bi-racial community of Southern Alabama, confirmed that stroke incidence rates are higher for blacks than whites for all stroke types, and that subarachnoid hemorrhage patients are more frequently female and younger than other stroke patients. Fourteen percent of the cases in this study had hemorrhages (8% parenchymatous and 6% subarachnoid). Only 6% were diagnosed as atherothrombotic infarction, since angiographic verification was required for this diagnosis. Embolic infarcts (26%), lacunar infarcts (13%), and infarctions of unspecified cause (40%) comprised the remaining cases. CT Scans were part of the diagnostic work up of 80% of the patients in this population-based study.

The studies conducted during the pilot phase have helped to guide the main phase research. During this past year study designs were completed for the

major research areas of the Stroke Data Bank. These areas include the characterization and clinical course of subtypes of stroke; stroke in evolution; a profile of the patient at high risk for complications; prediction of outcome based upon early activities of daily living; utilization of CT scans and arteriography; behavioral factors influencing stroke recovery; and economic consequences of stroke. In addition, the diagnostic categorization begun during the pilot and based upon laboratory findings as well as neurologic symptoms, has evolved into a decision tree to aid reliability and consistency of diagnosis.

The forms and definitions have been revised, and data collection will begin during July, 1983. Much effort has been spent in designing computerized quality control monitoring reports for the data banks.

OBFS held a workshop on the pilot Stroke Data Bank in conjunction with the Stroke Council of the American Heart Association in February, 1983. There was much interest in the establishment of Auxiliary Data Bank Centers. These centers would, under their own funds and management, collect an abbreviated version of the Stroke Data Bank forms. In addition, there would be an annual meeting to provide a forum for discussion of research ideas and findings.

The Traumatic Coma Data Bank was in a transition from pilot to main phase during this past year. Four academic neurosurgical centers have been awarded contracts for the main phase.

The pilot Traumatic Coma Data Bank gathered data on 581 accident victims. Of these, 58 were patients less than 15 years old. "The National Pilot Traumatic Coma Data Bank, A profile of Head Injuries in Children" will be published by Raven Press as part of the Proceedings from the 1982 Charlottesville Head Injury Meeting. Children differed from older accident victims with repect to mechanism of injury, (more pedestrian injuries and falls occurred to children), sex ratio (2:1 boys to girls, but 3:1 men to women), and outcome (33% mortality by hospital discharge for children versus 46% mortality for older patients). Although this study confirmed that children are more apt to survive severe head trauma than adults, a substantial case fatality rate among children was found.

Two papers from the pilot phase will be published in the August, 1983 issue of the Journal of Neurosurgery. The first, "The National Traumatic Coma Data Bank I: Design, Purpose, Goals, and Results" is a descriptive paper. The second, "Patients Who Talk and Deteriorate", details the clinical course of lucid patients who worsen. Out of the first 325 patients in the pilot Traumatic Coma Data Bank, 34 patients followed this course. Midline shift noted on CT scanning was found to be a particularly important sign for determining post-traumatic worsening.

Ongoing studies of pilot Traumatic Coma Data Bank patients include a study of 34 epidural hematoma patients, 48 patients with ventricular enlargement (suggesting hydrocephalus), and 50 survivors administered neuropsychological tests at 3 and 6 months post injury. In addition, studies of the impact of hypoxia, shock and increased intracranial pressure on survival, and of the predictive value of age, Glasgow Coma Score and pupillary response on mortality are in progress.

As one future initiative in clinical data banks, OBFS is exploring MS data resources in Switzerland. There is an MS registry in Zurich with MS case histories in excess of 6,000 patients. Many of these records are updated each year with comprehensive annual neurological examinations, and with autopsy reports when these patients die. Switzerland ostensibly has a well-funded MS Society seeking opportunities to fund researh in MS. OBFS has initiated discussions with a Swiss neurologist to process, examine, and accomplish a number of research studies with the retrospective data; and to present a proposal to establish an MS clinical data bank in Switzerland at an international meeting on MS to be held there in 1984 in Zurich, if Swiss funding can be arranged for the prospective collection of MS clinical data.

This time frame would be propitious for permitting a prior demonstration of the scientific value of the stroke data bank, and the time commitment of OBFS personnel in the data banks will have passed its peak. The participation of an external funding group to support the clinical portion of the data banks would relieve the Institute of the bulk of any fiscal burden.

OBFS continues collaboration with DNB, (CDNDP), on the clinical trial of cognitive and developmental effects of phenobarital on children with febrile seizures. OBFS is the statistical coordinating center for this trial and provides statistical analysis of the data.

In collaboration with DNB, OBFS conducted a survey of physicians to obtain information regarding the treatment and management of children who have had febrile seizures. All operational aspects of the survey were accomplished by OBFS, and it is expected that statistical analysis of the response data will be completed in early FY 84. In addition, OBFS staff consults actively on clinical trial design and serves on monitoring committees of extramurally funded clinical trials.

OBFS and DNB are conducting a prospective study of the prognostic value of the EEG for subsequent febrile seizures for children who have had a febrile seizure. OBFS is the statistical coordinating center for this large, population-based study being carried out in Yugoslavia, and is responsible for the data management and the statistical analysis. The clinical evaluation and data collection for the study are conducted by the Yugoslavian medical researchers.

A report developed by a committee of experts in response to a proposal for a workshop on measurement methodology of pain was submitted to the Program Directors. The committee recommended that NINCDS sponsor a multidisciplinary forum to identify and explore scientific and clinical issues in pain measurement. On the basis of the recommendations made by the committee, a symposium in FY 1984 on the assessment and measurement of pain will be supported by a grant. A group of approximately forty scientists and investigators, national and international, in the related fields will participate in the symposium.

OBFS is working with CDP on a study of language development in congenitally deaf children. This project will evaluate three modes of communication taught congenitally deaf children. Reading, writing and language comprehension tests will be given to the adolescents of 16 to 17 years of age who meet the eligibility criteria. OBFS has collaborated with CDP to develop a data collection protocol and has responsibilities for data management and statisticial analysis for

this project. The data will include as well records on the deaf children in the available population who did not qualify for inclusion in the study, for purposes of comparison.

OBFS is collaborating also with CDP on a longitudinal cohort study in a defined population, probably in a school district, to determine the rate of development of hearing disorders.

OBFS is working with STP on the statistical and data management aspects of a Phase II dose-response study of naloxone in the treatment of worsening ischemic stroke. This study is a component of the STP Master Agreement, and OBFS anticipates collaboration with STP on other stroke studies supported by this mechanism.

OBFS has been asked to collaborate with DNB on studies on neonatology in low birthweight chilcren. The initial phase of this project will be a feasibility study with subsequent phases dependent upon preliminary findings. OBFS will provide data management and statistical analysis to support this project.

OBFS anticipates that its collaborative activities in clinical trials with other Programs will increase in the near future. OBFS has the staff to provide the statistical coordinating center for four major direct operations studies. Four are in operation now, and OBFS will collaborate with CDP on the new study of the modes of communication taught congenitally deaf children, as a new fiscal year replacement for one slated for completion at that time. In order to handle additional requests for clinical trials and other direct operation collaboration, OBFS has requested funding for an expandable external operations center, which would operate as a data coordinating center for OBFS, under the direction of its project officer statisticians. The Operations Center would perform some 12 operations required in these studies for project coordination, data management, and statistical report generation.

OBFS continues to collaborate on a large number of IRP studies, such as clinical trials, case-control studies, and PET and CT scan development and enhancement. These studies include evaluation of methods of bioassay, metabolic abnormalities in families with a child who survived Reye's Syndrome, the allometric forms and growth rates of various species of primates, and therapeutic trials for movement disorders. This level of activity will continue in the future, with the level associated in some degree with the number of statisticians available for this type of collaboration. These associations between intramural scientists and OBFS statisticians often persist. Once a collaboration has been established, it frequently continues in a series of study associations over time. OBFS considers this to be the best indicator of the quality of OBFS biostatistical support.

OBFS is engaged in a study of severe and debilitating headache. The study consists of two parts; a feasibility study and an area survey. Data from the feasibility study are now being analyzed and preliminary results show that the statistical technique of discriminant analysis can correctly classify most cases of headache into four major types on the basis of patient reported data. The planning and design of the area survey have been completed. The objectives of the study are to assess the etiological and environmental factors associated with the major idiopathic headache types, to investigate the association between headache symptoms and features, and to explore the development of a new classification system of headache.

OBFS participated in several studies of multiple sclerosis. Data from the National Multiple Sclerosis Survey were used to examine the pattern of remission/exacerbations for selected symptoms. In addition, a paper regarding the factors affecting employment among people with MS has been prepared, and a description of the symptomatology of MS is being prepared. The latter paper is being prepared in conjunction with the DADDP. The study to determine whether there is an unusually high incidence and prevalence of multiple sclerosis in Colorado is continuing.

The two series of data collection for a study of non-institutionalized dementia cases have been completed. OBFS is cooperating with researchers at the National Institute of Mental Health and the Johns Hopkins University Schools of Hygiene and Public Health in analyzing the data.

In collaboration with the CDP, a manuscript on the prevalence of hearing loss in the Framingham Heart Study cohort has been completed. With the National Heart Lung and Blood Institute, work has begun on the analysis of data to examine a possible association between hearing loss and risk factors for cardiovascular disease.

OBFS has considered the problem of obtaining morbidity statistics on the rare neurological disorders. A review of existing survey strategies for studying rare characteristics in populations will identify and describe the various survey strategies, and provide an assessment of their practicality. The completed review will be a source of information on which strategies might be selected and used in future surveys of rare neurological disorders. Concurrent with the preparation of this review, the OBFS has proceeded with initial plans for a survey of neurologists to ascertain the prevalence of some of the rare neurological disorders. Although no final decisions have been made, it is expected that the survey will make use of membership lists of neurological associations.

OBFS continues to analyze the data of the Copiah County Study, a prevalence survey of major neurological disorders in a biracial population. In collaboration with the Intramural Research Program and the University of Mississippi Medical Center, the Office is preparing research reports for publication in medical and epidemiological journals. A report on essential tremor has already appeared, while a report on cerebral palsy is in press. Reports on Parkinsonism and dementia are not yet in final form. Work has proceeded on analysis of epilepsy and stroke data.

The first set of Disease Reports, on Huntington's Disease and Parkinson's Disease, are nearing completion. These reports will provide the most recent statistical information on morbidity, mortality, and hospitalization. These reports are being prepared by researchers at the Indiana University School of Medicine and the University of Maryland School of Medicine.

OBFS is continuing its studies of stroke mortality. In cooperation with researchers at Duke University, analysis of multiple cause of death data (underlying versus associated cause of death) was used to examine the changes in life expectancy that would result if stroke could be eliminated as a cause of death.

OBFS has completed work on a large-scale study to test a casefinding strategy for capturing data on epileptics in the general population. This

strategy required the participation of pharmacies and physicians, and special precautions were taken to safeguard the privacy of the patients. The final reports of the project have been microfilmed by, and are available through the National Technical Information Service. The reports can be obtained in microfiche or paper copy.

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.

A report on the findings from the National Survey of Intracranial Neoplasms is ready for submission for publication.

A collaborative investigation of head injury was designed with OBFS andthe 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. NIH peer review approved the pilot phase. The pilot phase will be a comparative study of the two head-injured cohorts. Based on the results of the pilot study, the second phase may include a clinical trial of therapy for head-injured patients.

OBFS 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 worked 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. A major objective of OBFS would be to collaborate with the University of Puerto Rico in determining 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.

A significant OBFS 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, epilepsy, cerebral palsy, and maternal infection during pregnancy. Papers relating age of seizure onset to mental retardation and cerebral palsy and seizure type to likelihood of seizure recurrence, obstetric complications to the outcome of cerebral palsy and seizure disorders and the relationship of toxoplasmosis during pregnancy to childhood outcome are some of the papers presented or published during the current fiscal year.

In collaboration with the Developmental Neurology Branch, CDNDP, 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. Further analysis is planned to investigate whether this relationship is due to artifacts.

There are a myriad of statistical problems facing investigators engaged in neurological studies. A typical example would be that encountered when the Kurtzke outcome score is used as an endpoint measure in clinical trials of therapy for MS. Differences between adjacent Kurtzke scores do not represent equal differences in outcome, and these disparities create problems of data analysis. OBFS research in statistical methodology represents attempts to resolve these and other important statistical problems in neurological research.

Because of their multistudy workload, OBFS statisticians have only small time commitments for methodological research, but, in fact, they have succeeded in producing a number of important publications. Examples of recent and current OBFS research include three methods for addressing problems of patient accrual for clinical trials: (1) An improved method of sample size determination, (2) A technique to monitor patient accrual relative to the target sample size, and (3) A statistical method that indicates termination of patient accrual and appropriate analysis of the data from patients that remain in the curtailed trial. Another area of statistical activity is the development of early stopping procedures for sequential and group sequential trial designs. OBFS statisticians have also devised new nonparametric tests for trends in data. The tests are especially applicable for evaluation of data related to neurological diseases with progression, and when patients are repeatedly evaluated over time.

Two opportunities for the development of new statistical methods arose from collaboration with IRP. A comparative study of bioassay methods resulted in an analysis of variance model that departed from the usual distributional assumptions. A likelihood ratio test was developed to account for the exponential nature of the experimental error. The second IRP study required a repeated measurement model to evaluate the difference between clinical and computerized testing of movement disorders.

To sum, OBFS has a vigorous program of research, both in collaboration with other programs, as well as in pursuit of its own programmatic initiatives. Its collaboration extends to many intramural and extramural research groups throughout the Institute, as well as to centers outside NINCDS. The scope of its research activities is also quite broad, and ranges from small, one-on-one collaborations with intramural scientists, to the conduct of large-scale, multicenter clinical data banks. OBFS has a relatively small, but important and continuing contribution to statistical methodology development applicable to neurological research.

OBFS Bibliography

Anderson, D.W. and Mantel, N.: On epidemiologic surveys. Am. J. Epidemiol. (In press).

Anderson, D.W., Miller, J.D., Kalsbeek, W.D.: Findings from a major U.S. survey of persons hospitalized with head injuries. Public Health Rep. 98: 475-478, 1983.

Baum, H.M. "Stroke prevalence: An analysis of data from the 1977 National Health Interview Survey." Public Health Rep. 97: 24-30, 1982.

Baum, H.M. and Goldstein, M. "A study of cerebrovascular disease type specific mortality: 1968-1977 Stroke. 13: 810-817, 1982.

Baum, H.M. and Rothschild, B.B. "Mobility restriction and multiple sclerosis." Arch. Phys. Med. Rehabil. (In press).

Dambrosia, J.M. and Greenhouse, S.W., "Early Stopping for Sequential Restricted Tests of Binomial Distributions." Biometrics, September 1983.

Ellenberg, J.H.: Ethical Guidelines for Statistical Practice - A Historical Prospective." The American Statistician. 1-4, February 1983.

Ellenberg, J.H., Hirtz, D., Nelson, K.B. "The Age of Onset of Seizures in Young Children." Annals of Neurology. (In press).

Goldstein, M. and Chen, T.C., "The Epidemiology of Disabling Headache." Advances in Neurology. 33: 377-390, 1982.

Gross, C.R., Kase, C.S., Mohr, J.P., Cunningham, S.C. and Baker, W.E: "Stroke in South Alabama: Incidence and Diagnostic Features - A population based study". Stroke. (In press).

Gross, C.R., Kunitz, S.C., Wolf, C. and Jane, J.A. "The National Pilot Traumatic Coma Data Bank: A profile of head injuries in children". In Winn, R. and Jane, J. (Eds.): In the Proceedings of the Fifth Conference on Neural Trauma, Raven Press. (In press).

Haerer, A.F., Anderson, D.W., Schoenberg, B.S.: Prevalence of essential tremor: Results from the Copiah County Study. Arch Neurol. 39: 750-751, December 1982.

Haerer, A.F., Anderson, D.W., Schoenberg, B.S.: Prevalence of cerebral palsy in biracial population of Copiah County, Mississippi. Dev Med Chil Neurol. (In press).

Hirtz, D., Nelson, K.B., Ellenberg, J.H. "Seizures following childhood immunizations." Pediatrics. 102: No. 1, 14-18, 1983.

Kunitz, S.C., Fishman, I.G., and Gross, C.R., "Attributes of Data Banks for Clinical Research: An Experience Based Approach". In Blum, B.I. (Ed.): In Proceedings of the Sixth Annual Symposium on Computer Applications in Medical Care. November 1982, pp. 837-841.

Lee, Y.J.: "Interim Recruitment Goals in Clinical Trials." J. of Chronic Disease. 36: No. 5, 379-389, 1983.

Lee, Y.J.: Quick and Simple Approximations of Sample Sizes for Comparing Two Independent Binomial Distributions: Different Sample Size Case. Biometrics. (In press).

Lee, Y.J.: Tests of Monotone Trend in k Poisson Means. J. of Quality Tech. (In press).

Lee, Y.J. and Dudewicz, E.J. "Robust selection procedures based on vector ranks." Statistics and Decisions. (In press).

Lee, Y.J. and Dudewicz, E.J. "Robust/Nonparametric Selection Methods in Blocked Data: Relative Efficiency Study." (In press).

Manton, K.G., and Baum, H.M.: The decline in cerebrovascular disease mortality 1968-1978: some observations and implications. Submitted to Stroke.

Marshall, L.F., Becker, D.P., Bowers, S.A., Cayard, C., Eisenberg, H., Gross, C.R., Kunitz, S.C., et al. "The National Traumatic Coma Data Bank, Part 1: Design, purpose, goals & results." J. Neurosurgery, 59: 1983. (In press).

Morgenthaler, D., Brooks, R.A., Talbert, A.J.: Polychromatic and Monochromatic x-ray beams in computed tomography". Physics in Medicine and Biology. (In press).

Nelson, K.B. and Ellenberg, J.H. "An Epidemiologic Approach to the Problems of Cerebral Palsy." Excerpta Medica, Neurology and Neurosurgery, 341-350, 1982.

Nelson, K.B. and Ellenberg, J.H. 'Maternal Seizure Disorders, Outcome of Pregnancy, and Neurologic Problems in Children." Neurology, 1274-1254, November 1982.

Nelson, K.B. and Ellenberg, J.H. "Obstetric Conditions, Apgar Scores and Neurologic Outcome." Journal of the American Medical Association. (In press).

Nelson, K.B. and Ellenberg, J.H. "Children Who Outgrew Cerebral Palsy." Pediatrics. 69: No. 5, 529-536, 1982.

Ward, C.D., Sanes, J.N., Dambrosia, J.M., and Calne, D.B.: "Methods for Evaluating Treatment in Parkinson Disease." In Fhan, S., Calne, D., and Shouloon, I. (Eds.): In Experimental Therapeutics of Movement Disorders. Raven Press, 1982, pp. 1-7.

Weiss, W. and Dambrosia, J.M.: "Common Problems in Designing Therapeutic Trials in Multiple Sclerosis". Arch. of Neurology. (In press).

Weiss, G., Talbert, A., and Brooks, R. "Use of Phantom Views to Reduce CT Streaks." Journal of Physics in Medicine and Biology. 27: No. 9, 1151-1162, 1982.

Woyciechoswka, J., Dambrosia, J. Tzan, N., and Madden D.: Multiple Sclerosis: Antiviral Antibodies. The Lancet, Vol. II, No. 8313, 1461-1462, 1982.

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1983

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

Date Contracts Initiated: July 1, 1982

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

Current Annual Levels FY'83:
1. $203,801
2. $200,004
3. $208,123
4. $180,552

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 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 subclassifications 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 prototype for national data bank networks for other neurological disorders.

Proposed Course of the Project: This is the second year of a five-year project. The initial course has included 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 has been very useful to the Full Phase Project, but the investigators are also being innovative in their approach to the best research use of the system.

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1983

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'83

1. -0-
2. -0-
3. -0-
4. -0-

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 in 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 has been analyzed.

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 are 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 high organized data handling capacity.

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1983

1. UNIV. OF TEXAS-GALVESTON AND BAYLOR UNIV. MEDICAL COLLEGE (NO1-NS-3-2339)

2. UNIV. OF CAL. IN SAN DIEGO (NO1-NS-3-2340)

3. MEDICAL COLLEGE OF VIRGINIA (NO1-NS-3-2341)

4. UNIV. OF VIRGINIA (NO1-NS-3-2342)

Title: Full Phase Traumatic Coma Data Bank

Contractors' Principal Investigators
1. Dr. Howard Eisenberg
2. Dr. Lawrence Marshall
3. Dr. Donald Becker
4. Dr. John Jane

Current Annual Level FY'83
1. $162,264
2. $197,311
3. $139,722
4. $145,000

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

Methods Employed: The Steering Committee, composed of the Principal Investigators and OBFS personnel, will meet, during the initial phase of this project, to outline the research objectives. Forms will be revised and a new data collection protocol will be established.

Significance to the NINCDS Program and Biomedical Research: The Traumatic Coma Data Bank projects are important for several reasons. Longitudinal data in severely head-injured traumatic coma victims will be collected at four centers, using uniform definitions 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 or 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 is the first year of a five-year project.

CONTRACT NARRATIVE
Office of Biometry & Field Studies, OD, NINCDS
Fiscal Year 1983

BETH ISRAEL HOSPITAL (N01-NS-2-2308)
BOSTON, MASSACHUSETTS

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

Date Contract Initiated: September 30, 1982

Contractor's Project Director: Dr. Howard Bleich

Current Annual Level FY'83: $218,006

Objectives: Beth Israel Hospital is the Data Bank Maintenance Contractor (DBMC) for the Stroke and Traumatic Coma Data Bank Networks. The system provides the host computer for these projects for data editing, DBMC storage, and retrieval, as part of the MISAR Medical Information Retrieval System. Data collected at hospital centers and entered into separately maintained Stroke and Coma data banks are available for retrieval within and among the centers.

Major Findings: The DBMC has created the computer data dictionary for the Stroke uniform vocabulary and developed methods for entering these data, as transmitted from the microprocessors located in each hospital, into the central data bank. The data dictionary defines the data elements contained in the patient chart. Data entry personnel at the clinical centers were trained. A pretest was performed to test out retrieval capabilities. Required enhancements will be implemented to meet the needs of the data bank projects.

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 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 the Stroke project. The Coma data bank clinical center contracts have recently been awarded. The DBMC will create the coma data dictionary and perform a pretest for coma data collection, entry and data analysis.

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1983

RLR & ASSOCIATES, INC., Fairfax, Virginia (NO1-NS-2-2315)

Title: Front-end Microprocessor Support for Data Bank Projects

Contractor's Project Director: Robert L. Rush

Current Annual Level: $71,402

Objectives: To provide the medical data bank projects with a software package for cost-efficient data entry, updating, editing and nighttime transmission to the host computer to implement patient management tools to aid the clinical centers with patient care.

Major Findings: The pilot studies yielded over 1700 patients in the two Data Banks. New procedures are being developed and will be implemented to enhance the front-end capabilities.

Significance to Biomedical Research and the Program of the Institute: The front-end is an integral part of the National Data Bank Projects, which were established to collect and maintain medical data for both patient management and clinical research.

Proposed Course of the Project: This project will continue throughout the Main Phase Stroke and Traumatic Coma Project.

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1983

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 1983

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

Title: ECA Dementia Supplement

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

Current Annual Level: $ 0

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.

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1983

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: $0

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 and pilot study have been completed. The Contractor has recommended a design for a national survey.

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. This study is now completed, and the Contractor's reports are available through the National Technical Information Service (Accession No. PB83-186304).

CONTRACT NARRATIVE
Office of Biometry and Field Studies, OD, NINCDS
Fiscal Year 1983

WESTAT, INC., Rockville, Maryland (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 - 0

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 have been 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. This contract has now been completed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02493-03 OBFS

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Stroke Diagnosis: The Pilot NINCDS Data Bank Algorithm

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Selma Kunitz, Head, Computer Applications Section, OBFS, NINCDS

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	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

In conjunction with the NINCDS Pilot Stroke Data Bank Network (Z01 NS-02238-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 have been analyzed. A manuscript describing the pilot Data Bank and explaining the algorithm is in preparation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02499-03 OBFS

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Stroke Incidence in South Alabama

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Cynthia Gross, Ph.D., Biostatistician, OBFS, NINCDS

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 *(Use standard unreduced type. Do not exceed the space provided.)*

As a component of the Pilot Stroke Data Bank (NO1 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. This project has been completed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02443-04 OBFS

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Development of Offline Data Entry System for Stroke and Coma Projects

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Barbara Nichols, Computer Specialist, CAS, OBFS, OD, NINCDS

COOPERATING UNITS *(if any)*
None

LAB/BRANCH
Office of Biometry and Field Studies

SECTION
Computer Applications 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 *(Use standard unreduced type. Do not exceed the space provided.)*

A "front-end" general purpose software package was developed for the Datapoint terminals in the Data Bank Clinical 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, requested items and special formats such as dates. Prior to data transmission the package provides relational checks for data inconsistencies and produces error messages for the clinical centers to facilitate correction. A cost-efficient communication discipline has been 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 Centers.

The front-end support team provides all user documentation and is available on a daily basis for any assistance needed by the clinical centers.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02596-01 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Data Bank Maintenance Center

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)

Barbara Nichols, Computer Specialist, CAS, OBFS, OD, NINCDS

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Office of Biometry and Field Studies

SECTION

Computer Applications Section

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD 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 *(Use standard unreduced type. Do not exceed the space provided.)*

The Data Base Maintenance Center (DBMC) stores and maintains clinical data for the Stroke and Traumatic Coma Data Banks. The objectives of the Data Bank Projects are to efficiently collect, store, retrieve and manage clinical data in order to carry out research on cerebrovascular disease and to identify the course of traumatic coma and patterns of survival and recovery.

The DBMC receives the data via nighttime transmission from the data bank clinical centers. The maintenance center provides an existing, flexible computer system with a set of programs that examines trends and relationships among data items. Descriptive statistical programs such as frequency counts, scatter plots and cross-tabulations are provided as part of the software package. In addition, the DBMC provides utility programs for creation of files to interface with standard statistical packages such as the Statistical Analysis System (SAS) and the Statistical Package for the Social Sciences (SPSS).

The DBMC provides all program documentation and site training at the clinical centers on the use of the system and has staff available on a daily basis for any assistance needed by the clinical centers or OBFS.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02498-03 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

CT Scan Observer Variability Study

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)

Cynthia Gross, Ph.D., Biostatistician, CAS, OBFS, NINCDS

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 *(Use standard unreduced type. Do not exceed the space provided.)*

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 02340-06 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. The application of Kappa statistics to this type of study is widespread, yet the restrictive assumptions of this method are rarely met. An extension of the usual methods, to allow for a fixed, not random, set of raters, is being developed, based upon the work of Davies and Fleiss (Biometrics, 1982).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02598-01 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Complications, Recurrence, and Outcome: Stroke Data Bank

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)

Cynthia R. Gross, Ph.D., Biostatistician, CAS, OBFS, OD, NINCDS

COOPERATING UNITS *(if any)*

Department of Neurology, Boston U. Medical Center, Boston, Massachusetts

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 *(Use standard unreduced type. Do not exceed the space provided.)*

The majority of stroke patients will survive the acute episode; some will recover to their pre-stroke levels of functioning; and others will be disabled to some degree. Complications following stroke may result from the insult itself or be related to diagnostic or therapeutic methods used in stroke management. Complications may prolong a patient's hospital stay and affect his ultimate outcome. Data from the Stroke Data Bank (NO1-NS-2-2302, NO1-NS-2397, 98, 99), a prospective, multicentered, study of hospitalized stroke patients, will be used to profile the complications - prone patient. Socio-demographic and clinical data, including age, sex, location and type of stroke, severity and type of initial deficit(s) will be compared with occurrence of complications such as seizures, visceral bleeding and stroke recurrence to characterize those patients who experience complications. The clinical course of those patients with complications will be studied in order to determine the input of complications on outcome.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02599-01 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Behavioral Factors Influencing the Recovery from Stroke

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Selma C. Kunitz, OBFS, OD, NINCDS

COOPERATING UNITS *(if any)*

Boston University, Philip Wolf, M.D.; University of Maryland, Tom Price, M.D.; Michael Reese Medical Center, Lou Caplan, M.D.; University of South Alabama, Jay Mohr, M.D.

LAB/BRANCH

Office of Biometry and Field Studies

SECTION

Computer Applications Section

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.20	.20	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

In order to better comprehend the factors influencing recovery from Stroke, behavioral factors will be studied, utilizing the Stroke Data Bank population (NO1-NS-2-2302, NO1-NS-2-2397,98,99). Specifically, two dimensions of social support will be looked at with respect to stroke outcome. The two dimensions are source, (family and institutional)and type,(affective and instrumental). Patients will be stratified by stroke severity. Definition of outcome will include Activities of Daily Living (ADL) and social functioning.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02491-03 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Activities of Daily Living Following Stroke

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

P. Wolf, Department of Neurology, Boston University

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)

- [X] (a) Human subjects
  - [ ] (a1) Minors
  - [ ] (a2) Interviews
- [ ] (b) Human tissues
- [ ] (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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 followup. This project has been completed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02587-01 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Utility of Diagnostic Tests in Predicting Stroke Mechanism and Outcome

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

PI: Dallas W. Anderson Survey Statistician OBFS NINCDS

COOPERATING UNITS *(if any)*

Michael Reese Hospital and Medical Center, Chicago, IL

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 *(Use standard unreduced type. Do not exceed the space provided.)*

A variety of diagnostic tests (including angiography, CT scanning, and noninvasive cardiac and vascular tests) are available for the study of the stroke patient. These tests vary with respect to cost, discomfort, and risk of complication. We propose to investigate the utility of each of these tests in establishing stroke cause. Deciding on stroke cause is essential to planning effective therapy. Furthermore, we will examine the utility of these tests in predicting survival, rate and degree of recovery, and risk of stroke recurrence. We also propose to establish those circumstances in which each test is likely to be helpful and those instances in which the test should be deferred because of low ratio of benefit to either cost or risk of complications.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02492-03 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Stroke Diagnosis and Prognosis Based on the NINCDS Data Bank

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)

Lawrence V. Rubinstein, Mathematical Statistician, SMS, OBFS, OD, NINCDS

COOPERATING UNITS *(if any)*

Boston University Medical Center, New York Neurological Institute, University of Maryland Hospital, Michael Reese Hospital, Beth Israel Hospital

LAB/BRANCH

Office of Biometry and Field Studies

SECTION

Mathematical Statistics

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

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

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The Pilot Stroke Data Bank project has developed operational diagnostic algorithms for the classification of stroke type. These algorithms are based on the type of laboratory evidence available (CT, angiography, etc.), its findings, and the severity of stroke as measured by the neurologic exam.

In this study, the usefulness of these diagnostic algorithms in differentiating etiology and predicting outcome is evaluated.

The correlation of various factors relating to apparent etiology, stroke severity, and long-term prognosis is measured also.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02590-01 OBFS

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Evolving Stroke

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
J.M. Dambrosia, Acting Chief, SMS, OBFS, OD, NINCDS

COOPERATING UNITS *(if any)*
Computer Applications Section, OBFS
University of Maryland, Boston University, Michael Reese Hospital, Columbia University

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 *(Use standard unreduced type. Do not exceed the space provided.)*

This study is one of a number of research components of the Stroke Data Bank Project. Based on prospectively collected patient data, a temporal description of stroke in evolution by type and site of lesion will be developed. The patients' clinical status determined by changes in Glasgow Coma Score, hemiparesis score, and stroke severity score identify those cases that evolve. This study also attempts to identify factors that cause or contribute to stroke evolution. Some of these are: edema, shock, electrolyte imbalance, cardiovascular factors and cognitive problems.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02340-06 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Pilot Data Bank Network Project in Coma

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Selma C. Kunitz, Chief, Computer Applications Section, OBFS, OD, NINCDS

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

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 *(Use standard unreduced type. Do not exceed the space provided.)*

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. The pilot project has been completed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02516-02 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Traumatic Coma: Epidemiological Characteristics

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)

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

COOPERATING UNITS *(if any)*

None

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 *(Use standard unreduced type. Do not exceed the space provided.)*

The pilot Traumatic Coma Data Bank has collected information on 581 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. By profiling the characteristics of the 58 children in the data bank, it was found that pedestrian accidents were the most frequent cause of injury and that falls were most common among infants and toddlers. The sex ratio varied with age being 2:1 (male excess) in children, almost 4:1 in the middle ages and about 1:1 in the 60 and older age group. Case fatality rates also differed by age, but not by sex.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02408-05 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Clinical Data Banks as a Resource for Epidemiologic Research

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)

Cynthia Gross, Ph.D., Biostatistician, CAS, OBFS, OD, NINCDS

COOPERATING UNITS *(if any)*

None

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 *(Use standard unreduced type. Do not exceed the space provided.)*

Much has been written on the use of observational studies in epidemiological research. It is necessary to apply many of the same epidemiologic techniques used in conventional observational study designs to the clinical data bank. Work on determining which epidemiologic approaches are most appropriate for use with clinical data banks was begun in conjunction with the Pilot Stroke and Traumatic Coma Data Bank Networks (NO1-NS-8-2309, 6, 7, 8; NO1-NS-9-2302, 96, 97, 98) and is continuing with the full phases of these projects. In the past, this project has focused upon quality assurance methods; at present, the emphasis is on epidemiological considerations in the analysis and interpretation of data bank results.

Aspects under study include 1) generalizability of results from multicentered hospital-based cases, 2) methods for detecting inter-center variation and determining conditions when pooling of results is appropriate, and 3) use of the data bank as a source of cases for case-control studies.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02595-01 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Methodological Aspects of Data Banks

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Irene G. Fishman, 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, 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 *(Use standard unreduced type. Do not exceed the space provided.)*

Data Banks have been developed in Stroke and Traumatic Coma. The organizing principles behind establishing a data bank for description of a neurologic condition requires proposing and testing entirely new concepts of data management. This study analyzes the underlying organizational and methodological principles which are necessary for optimal functioning of a data bank.

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, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Medical Studies Database System

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)

Karlin Richardson, Systems Programmer, CAS, 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:
.3	.3	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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 the RTE 6/VM operating system;

3) A forms-tracking system which records the validity status of the data;

4) Dictionary driven range and relational validity checks;

5) Easy-to-use time-oriented subsetting and retrieval utilities.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02597-01 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Reliability and Validity of Data Collection Methodology in the Stroke Data Bank

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)

David Shinar, Psychologist, CAS, OBFS, NINCDS

COOPERATING UNITS *(if any)*

Depts. of Neurology in BU School of Medicine, Michael Reese Hospital, Univ. of Md. Hospital, and Univ. of So. Ala. College of Medicine and the Dept. of Computer Medicine, Beth Israel Hospital.

LAB/BRANCH

Office of Biometry and Field Studies

SECTION

Computer Applications Section

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.7	.7	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Current human factors evaluation of data collection procedures and monitoring used in the pilot study has already resulted in changes to be implemented in the Full Phase Stroke Data Bank Study. These involve areas of forms, design, formulation of questions, and data collection, feedback and monitoring procedures.

Shortly after data collection starts, the reliability and validity of key data items will be assessed, intercenter variability will be measured and criteria of accuracy will be determined and used as objectives in data quality.

The reliability assessments will involve intercenter comparisons and test-retest techniques. The validity assessments will involve comparisons of innovative procedures vs. standard procedures.

Focus areas include stroke diagnosis, CT Scan and angiography analyses, and functional assessments. Recommendations for improvements in data collection methodology will be made.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02496-03 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Preliminary Steps for a Data Bank Project in Epilepsy

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Selma C. Kunitz, Chief, CAS, OBFS, NINCDS

COOPERATING UNITS *(if any)*

None

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 *(Use standard unreduced type. Do not exceed the space provided.)*

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. This project has been completed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02444-04 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Statistical coordinating center for the phenobarbital clinical study*

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Young Jack Lee, Mathematical Statistician, SMS, OBFS, OD, NINCDS

COOPERATING UNITS *(If any)*

Cerebral Palsy and Other Motor Disorders Section, DNB, CDNDP, 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 *(Use standard unreduced type. Do not exceed the space provided.)*

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, CDNDP, NINCDS, and the contractor of the study is the University of Washington.]

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02411-05 OBFS

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Survey of Practice in the Management of Febrile Seizures

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Young Jack Lee, Mathematical Statistician, SMS, OBFS, OD, NINCDS

COOPERATING UNITS *(if any)*
Cerebral Palsy and Other Motor Disorders Section, DNB, CDNDP, 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)

- [X] (a) Human subjects
- [ ] (b) Human tissues
- [ ] (c) Neither
- [ ] (a1) Minors
- [ ] (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A survey of clinical practice in the management of febrile seizures is ongoing. The survey questionnaire was sent to 10,000 physicians. The questionnaire is now being entered into the DCRT/NIH computer. The analysis of the survey data 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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02483-03 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Predictive Value of the EEG in Febrile Seizures

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Lawrence V. Rubinstein, Mathematical Statistician, SMS, OBFS, OD, NINCDS

COOPERATING UNITS *(if any)*

Pediatric Clinic, University of Skopje, Yugoslavia

LAB/BRANCH

Office of Biometry and Field Studies

SECTION

Mathematical Statistics

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 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 *(Use standard unreduced type. Do not exceed the space provided.)*

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. By the end of FY'83, approximately 200 patients were registered into the study and began the study protocol and follow-up.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02504-03 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Epidemiological Study of Pain*

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)

Ta-Chuan Chen, Ph.D., Mathematical Statistician, OBFS, OD, 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 *(Use standard unreduced type. Do not exceed the space provided.)*

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 syndromes with various demographic, psychological and medical-care variables will be investigated.

*This project was formerly titled "Estimation of the Incidence Rate of Disabling and Severe Headache".

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02517-02 OBFS

PERIOD COVERED: October 1, 1982 through September 30, 1983

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.): Statistical Methodology for the Measurement of Pain

PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages.)

(Name, title, laboratory, and institute affiliation): Ta-Chuan Chen, Ph.D., Mathematical Statistician, OBFS, OD, NINCDS

COOPERATING UNITS (if any): None

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
  - ☐ (a1) Minors
  - ☐ (a2) Interviews
- ☐ (b) Human tissues
- ☒ (c) Neither

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

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, β, 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. An external committee has reviewed the current state-of-the-art of the methodology for the measurement of pain. This meeting recommended that a full-scale symposium be supported to discuss various aspects of pain measurement problems. A grant proposal will be submitted to fund the symposium.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02594-01 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Factors Predictive of Reading and Writing Skills in the Congenitally Deaf*

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Young Jack Lee, Mathematical Statistician, SMS, 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, 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 *(Use standard unreduced type. Do not exceed the space provided.)*

This study is to determine the factors predictive of the development of reading and writing skills in the congenitally deaf. The analysis of the effects of three different approaches to preschool language training in the congenitally deaf is planned. The three approaches to be studied are: 1) American sign language, 2) Speech training with augmentation of residual hearing, and 3) Total communication combining sign language and speech training.

*[This study is the OBFS/NINCDS portion of the CDP contract study. The RFP number is NIH-NINCDS-83-19. The project officer of the project is Dr. Christy Ludlow, CDP, NINCDS].

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02484-03 OBFS

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Statistical Coordinating Center for Communicative Disorders Program Projects*

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Young Jack Lee, Mathematical Statistician, SMS, 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:
.10	.10	0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The project is to study factors predictive of reading and writing skills in the congenitally deaf. The RFP for this project is available now.

*[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.]

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02490-03 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Research in Statistics

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)

James M. Dambrosia, Acting Chief, SMS, OBFS, OD, NINCDS

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Office of Biometry and Field Studies

SECTION

Mathematical Statistics

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.65	.65	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02591-01 OBFS

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Reye's Syndrome Study

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Young Jack Lee, Mathematical Statistician, SMS, 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:
.15	.05	.10

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The Infectious Diseases Branch is studying salicylate metabolism, other clinical chemistries and histocompatibility antigens in the family with Reye's Syndrome patients who have completely recovered from the syndrome. OBFS is responsible for all statistical components of the study including data analysis and statistical modeling of the clinical chemistry data.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02486-03 OBFS

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Statistical models of in vitro mutagenicity assays

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Young Jack Lee, Mathematical Statistician, SMS, OBFS, OD, NINCDS

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 *(Use standard unreduced type. Do not exceed the space provided.)*

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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02482-03 OBFS

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Optimization of Software for PET Scanner*

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Alan J. Talbert, Statistician, SMS, OBFS, OD, 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 *(Use standard unreduced type. Do not exceed the space provided.)*

The software which has been written is in regular use in clinical and research applications of the Neuro-PET. The programs are being refined, debugged, optimized, and documented.

*[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, IRP, NINCDS.]

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02415-05 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Cage Standards for Primates

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory and institute affiliation)

James Dambrosia, Acting Chief, SMS, 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:
0.10	0.05	0.05

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects
  - ☐ (a1) Minors
  - ☐ (a2) Interviews
- ☐ (b) Human tissues
- ☒ (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02404-05 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

National Survey of Chronic and Debilitating Headache

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Frederic D. Weinfeld Survey Statistician OBFS NINCDS

COOPERATING UNITS *(if any)*

Nat'l. Center for Health Stat.; 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 *(Use standard unreduced type. Do not exceed the space provided.)*

The purposes of this study are to identify and assess the etiological and environmental factors associated with the major idiopathic headache types, to investigate the association between headache symptoms and features, to explore the development of a new classification system of headache, to measure the prevalence, and to describe the demographic characteristics of the major types of headache. To this end a survey of the general population has been designed. The survey questionnaire, which includes sections on demography, descriptive headache features, medical information, and history, has been developed. The study consists of two parts: a feasibility study and an area survey. In the feasibility study, patients from four headache clinics have participated in a telephone interview. Information in the physician files about the headaches has also been abstracted. The data are now being analyzed and preliminary results show that the statistical technique of discriminant analysis can correctly classify most cases of headache into four major types on the basis of patient reported data. The planning and design of the area survey has been completed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02495-03 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Analysis of Data From the National Survey of Multiple Sclerosis

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Herbert M. Baum Demographer OBFS NINCDS

COOPERATING UNITS *(if any)*

Demyelinating, Atrophic and Dementing Disorders Program; National Analysts; 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:
1.10	1.00	0.10

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The National Multiple Sclerosis Survey (NMSS) 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. We are still in the process of analyzing these data. Current efforts are focusing on mobilitiy restriction, factors affecting employment, symptomatology, and mean remission/exacerbation times for selected symptoms.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02494-03 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Prevalence of Multiple Sclerosis in Colorado

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Herbert M. Baum Demographer OBFS NINCDS

COOPERATING UNITS *(if any)*

The Rocky Mountain Multiple Sclerosis Center
University of Colorado School 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:
0.25	0.20	0.05

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02515-02 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Study of Hearing Disorders Among the Aged

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Eve K. Moscicki Scientist OBFS NINCDS

COOPERATING UNITS *(if any)*

Communicative Disorders Program
National Heart Lung and Blood Institute

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 *(Use standard unreduced type. Do not exceed the space provided.)*

The objectives of this project are to describe the prevalence of hearing impairment in the Framingham cohort by demographic characteristics, to investigate the relationship between the severity of hearing impairment and risk factors for hearing loss, and to examine possible relationships between hearing impairment and cardiovascular risk factors and events. Hearing data collected during Cycle 15 of the Framingham Heart Study (1978-1979) have been 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 are being examined.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02585-01 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Survey of Rare Neurological Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Frederic D. Weinfeld Survey Statistician OBFS 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:
.25	.25	.00

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is to design and conduct a survey which would measure the prevalence and describe the demographic characteristics of persons with rare neurological disorders and identify the clinical factors which are associated with these disorders. Initial plans are being made for a relatively inexpensive survey of neurologists to ascertain the prevalence of some of the rare neurological disorders. Although no final decisions have been made, it is expected that the survey will make use of membership lists of neurological associations.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02586-01 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

An Examination of Multiple Cause of Death Data for Stroke

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Herbert M. Baum Demographer OBFS NINCDS

COOPERATING UNITS *(if any)*

Center for Population Studies, Duke University

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:
0.60	0.50	0.10

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has three main goals. First to determine whether a change in the coding of a stroke as underlying versus as an associated cause of death is partially responsible for the large decline in the rates of stroke mortality as calculated from the underlying cause of death. Next, to construct life tables and estimate the impact of eliminating stroke as a cause of death; and lastly, to examine the pattern of multiple causes of death which occur for stroke.

Computer tapes, issued by the National Center for Health Statistics, containing all death certificates in the United States for the period 1968-1978 were used. All certificates where stroke (ICDA-8 Codes 430-438) was listed as either an underlying or associated cause of death were selected for study. The data were then tabulated by age, race, and sex. Life tables were constructed to estimate the change in life expectancy if stroke were eliminated as a cause of death.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02497-03 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

INDO-U.S. Study of Head Injury

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)

William Weiss, Chief, 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 *(Use standard unreduced type. Do not exceed the space provided.)*

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 has been peer-reviewed by NIH, and approval has been given to proceed with the pilot phase of the study.

Staff of OBFS and UVA will proceed to New Delhi, examine the quality of the data and return with the Indian data to be processed and analyzed together with the UVA data. The principal investigators will meet in New Delhi in the spring to review the pilot data and plan the second phase of the study.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02506-03 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Antibody Titers in Macacas on Cayo Santiago

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)

William T. London, Chief, Experimental Pathology Section, IDB, IR, 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:	PROFESSIONAL:	OTHER:
.05	.05	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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. The monkey colony on Cayo Santiago will be trapped in January of 1984, at which time the remaining monkeys will be bled and the antibody titers analyzed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02114-10 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Etiology and Natural History of Convulsive Disorders and Cerebral Palsy*

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Jonas H. Ellenberg, Deputy Chief, OBFS, OD, 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:
1.5	1.2	.3

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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 has been completed, including correlation and regression analysis. Manuscripts for a book in each area are in progress. 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 02059-11 DNB. The principal investigator for these studies is Dr. Karin B. Nelson, Chief, Cerebral Palsy and Other Motor Disorders Section, DNB, NDP, NINCDS.]

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02312-07 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Maternal Infection Study*

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)

Jonas H. Ellenberg, Deputy Chief, 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, 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 *(Use standard unreduced type. Do not exceed the space provided.)*

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 00402-27 ID. The principal investigator on the overall study is Dr. John L. Sever, Chief, IDB, IRP, NINCDS.]

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02505-03 OBFS

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Headache in Pregnant Women

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Ta-Chuan Chen, Ph.D., Mathematical Statistician, OBFS, OD, NINCDS

COOPERATING UNITS *(if any)*
Paul Nichols, Ph.D., Developmental Neurology Branch, CDNDP, 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 *(Use standard unreduced type. Do not exceed the space provided.)*

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 nonmigraine group. More intensive statistical analyses will be carried out to detect possible artifacts which may explain this apparent association.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02446-04 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Parkinson's Disease in Twins*

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

James M. Dambrosia, Acting Chief, SMS, OBFS, OD, NINCDS

COOPERATING UNITS *(if any)*

Experimental Therapeutics Branch, IRP
Section on Neuroepidemiology, ODIR, IRP

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 *(Use standard unreduced type. Do not exceed the space provided.)*

Twin pairs, discordant with respect to Parkinson's disease, are evaluated for zygosity and the presence of Parkinson's disease. Clinical, laboratory, historical, and psychometric data are obtained for both the proband and the co-twin. Statistical analysis of these matched pairs will attempt to identify risk factors and examine differences between the probands 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 02167-09 ODIR). The principal investigator on the overall study is Dr. Roswell Eldridge, NES, ODIR, IRP].

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02488-03 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Interactive Computer System for Patient Entry and Randomization*

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)

Young Jack Lee, Mathematical Statistician, SMS, 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, 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 *(Use standard unreduced type. Do not exceed the space provided.)*

An interactive computer system has been developed. The system utilizes the TSO of the DCRT, NIH computer. The clinical trial operations office can register patients entering a clinical trial, check the eligibility and perform random allocations of the treatment to eligible patients, all using the interactive system.

*Formerly titled "Interactive Computer System for Patient Entry and Randomization for Clinical Study".

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02489-03 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less: Title must fit on one line between the borders.)*

Evaluation of communicative disorders information by MEDLINE* †

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)

Young Jack Lee, Mathematical Statistician, SMS, 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, Maryland 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 *(Use standard unreduced type. Do not exceed the space provided.)*

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. Contract numbers are N01-NS-0-2342, N01-NS-0-2343, N01-NS-0-2344, N01-NS-0-2345 and N01-NS-0-2346].

†Formerly titled "Evaluation of the effectiveness of information services provided to specialists in communicative disorders by MEDLINE".

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02592-01 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Central Nervous System Metastases from Lung Cancer

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)

Lawrence V. Rubinstein, Mathematical Statistician, SMS, OBFS, OD, NINCDS

COOPERATING UNITS *(If any)*

Illinois Cancer Council; Mayo Clinic, Seattle Cancer Group; Toronto Cancer Group; UCLA Medical Center

LAB/BRANCH

Office of Biometry and Field Studies

SECTION

Mathematical Statistics

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 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 *(Use standard unreduced type. Do not exceed the space provided.)*

It has been determined by the Lung Cancer Study Group (LCSG) that central nervous system, in particular brain, metastases account for approximately 25% of first recurrences in Stage I lung cancer. In this study, prognostic factors and treatment effects relating to recurrence in the CNS, and the outcome for patients suffering CNS metastases, as investigated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02501-03 OBFS

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Myasthenia Gravis Study

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Irene G. Fishman, Statistician, 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 *(Use standard unreduced type. Do not exceed the space provided.)*

The project involved consultation to a group of neurologists who were interested in the possibility of collecting clinical information on patients with myasthenia gravis. An initial set of parameters to be collected was proposed, forms were redesigned, and data was being collected on demographics, initial evaluation, and subsequent follow-ups. OBFS staff acted only in a consultative role to this extramural group of investigators. This project has now been completed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02500-03 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Polymyositis/Dermatomyositis Study

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)

P.I.: Irene G. Fishman, Statistician, 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 *(Use standard unreduced type. Do not exceed the space provided.)*

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 was discussed at a meeting in the Fall, 1982. OBFS staff is acting in a consultative role to this extramural group of investigators.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02450-04 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1982

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Spinal Manipulative Therapy as Treatment for Athletes.*

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)

Peter Jokl, Assoc. Prof. of Orthopaedic Surgery, Yale Univ. School of Medicine

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:	PROFESSIONAL:	OTHER:
0.1	0.1	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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 requires 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 would participate in the study.

This project is presently in limbo due to lack of funds. OBFS will participate if an external source of funds such as the Olympic Medical Commission, decides to support the project. Otherwise the proposed study must be considered terminated.

*Formerly titled "Spinal Manipulative Therapy as Treatment for Musculo-Skeletal Dysfunction in Athletes".

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02239-07 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Design of Health Interview Survey Questionnaire Supplements

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

PI: Frederic D. Weinfeld Survey Statistician OBFS NINCDS

COOPERATING UNITS *(if any)*

National Center for Health Statistics, Hyattsville, MD

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	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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. This project has been terminated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02518-02 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neurological Aspects of Aging in Primates

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation) Manuel Martinez-Maldonado, Chief, Medical Service & Director Renal Metabolic Laboratory, VA Center, San Juan, Puerto Rico

COOPERATING UNITS *(if any)*

Medical School, Univ. of Puerto Rico, San Juan, PR; Vet. Admin. Center, San Juan, PR; 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 *(Use standard unreduced type. Do not exceed the space provided.)*

This project will be a grant-supported investigation 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. The OBFS contribution to the planning of this project has been completed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02405-05 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Strategies for Analyzing Data from Small Area Health Surveys

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

PI: Dallas W. Anderson Survey Statistician OBFS 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	.09	.01

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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 (Y01-NS-70031, N01-NS-7-2357). This project has been completed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02514-02 OBFS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Review of Techniques for Sampling of Rare Populations

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

PI: Dallas W. Anderson Survey Statistician OBFS 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	.09	.01

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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.

TAB 2 -- EXTRAMURAL ACTIVITIES PROGRAM -- EAP

ANNUAL REPORT

October 1, 1982 through September 30, 1983

Extramural Activities Program

National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

ANNUAL REPORT
October 1, 1982 through September 30, 1983
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: John C. Dalton, Ph.D.
Deputy Director: Donald H. Luecke, M.D.
Chief, Scientific Review Branch: Raymond Summers, Ph.D.
Chief, Contracts Management Branch: Lawrence J. Fitzgerald, Jr.
Chief, Grants Management Branch: Edward M. Donohue
Chief, Administrative Services Branch: John H. Jones

Staff carries out an overall coordinating and supervisory function in regard to the implementation of recommendations of the NANCDS Council and other advisory bodies, and the processing and issuance of proposals and awards in the respective program areas. The Director, EAP, in consultation with the Director of NINCDS, works closely with the other Program Directors on questions of policy relating to the NINCDS extramural programs and represents the Institute Director on these matters at the level of NIH.

More specifically, the Extramural Activities Program coordinates grant and contract programs for the NANCDS Council, the Program Directors and their staff and managers; the Scientific Programs Advisory Committee, the Contract Review Board, and the Training Board. 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., status of Training and Research Career Programs; and interacts with the OD, NINCDS, to provide fiscal information, e.g., Fiscal Status Reports, Percentage Funding Rates, and develops alternate strategies for various budget levels.

Several changes have occurred within the EAP: The former Office of Data Analysis and Reports (ODAR) has been relocated within the Office of Program Analysis, NINCDS, and renamed the Management Information and Data Section (MIDS). The close cooperation between MIDS and EAP continues as under the previous organization, but in addition provides the OD, NINCDS with better direct access to MIDS. The EAP now provides supervision of the Administrative Services Branch. A brief summary of this branch activity is to be found on page 9-EAP.

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, 1982 through September 30, 1983
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 improved diagnosis, treatment, and prevention of nervous system disorders, as well as disorders of the neuromuscular apparatus, the ear, and human communication. They include problems affecting the development and maturation of the nervous system (developmental disorders, motor and convulsive disorders, demyelinating and degenerative disorders); disorders caused by extrinsic insults (central nervous system infections, stroke, trauma, tumors); and disorders in human communication (hearing, speech, language, the vestibular system, other senses [e.g., taste and smell] 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 development awards, institutional research training grants, 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 '79	MAY '80	MAY '81	MAY '82	MAY '83
645	618	685	644	690

During this time, there have been increases in the total number of applications reviewed annually. This may be attributed in part, both to the veritable "explosion" of scientific interest in the neurosciences, and the effectiveness of the research training programs of the Institute from which the output of fully trained investigators has grown significantly.

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 '79	FY '80	FY '81	FY '82	FY '83
NUMBER	1,391	1,553	1,505	1,559	1,633
DOLLARS	$132.2	$160.7	$171.0	$181.0	$202.6

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

TYPE OF AWARD	PROGRAM AREAS** CD No.	CD Dollars	CDND No.	CDND Dollars	DADD No.	DADD Dollars	FN No.	FN Dollars	ST No.	ST Dollars	TOTAL No.	TOTAL Dollars
Research Grants	267	26.7	376	38.0	287	27.0	432	41.0	189	20.6	1551	153.3
Program Projects & Clinical Centers	19	11.8	13	7.8	18	10.8	0	0	32	18.9	82	49.3
Contracts	7	1.5	19	4.8	2	0.2	15	2.8	10	1.6	53	10.9
Training Grants	17	1.0	9	0.6	16	1.4	29	2.0	8	0.5	79	5.5
Fellowships	33	0.6	29	0.6	13	0.2	136	2.5	16	0.3	227	4.2
Teacher Investigator Development Awards	20	0.9	29	1.2	42	1.8	0	0	26	1.1	117	5.0
Research Career Development Awards	9	0.3	13	0.5	7	0.3	24	0.9	5	0.2	58	2.2
Research Career Awards	0	0	3	0.1	0	0	0	0	1	***	4	0.1
GRAND TOTAL	372	42.8	491	53.6	385	41.7	636	49.2	287	43.2	2171	230.5

*Dollars in millions
**CD = Communicative Disorders
CDND = Convulsive, Developmental & Neuromuscular Disorders
DADD = Demyelinating, Atrophic & Dementing Disorders
FN = Fundamental Neurosciences
ST = Stroke and Trauma
***Less than $50,000

October 1, 1982 - September 30, 1983

ANNUAL REPORT
October 1, 1982 through September 30, 1983
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 NRSA are funded from the $9,703 million available in the FY '83 budget for training. The other two programs, the Research Career Development Award and the Teacher Investigator Development Award, are funded from FY '83 funds available in the "Other Research" category.

National Research Service Awards for Institutional Grants (Training Grants)

From FY '83 funds, the Institute provided continuation support for 61 Institutional NRSA's and made 18 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	6	$ 408	11	$ 624	17	$1,032
Convulsive, Developmental & Neuromuscular Disorders	2	185	7	449	9	634
Demyelinating, Atrophic & Dementing Disorders	1	109	15	1,288	16	1,397
Fundamental Neurosciences	7	591	22	1,418	29	2,009
Stroke and Trauma	2	114	6	358	8	472
Total	18	$1,407	61	$4,137	79	$5,544

*Amounts in thousands

There continues to be a critical shortage of physician investigators in the neurosciences. An increasing number of training grant programs are offering excellent training opportunities for clinically trained persons. In addition, the NINCDS announced its intent to offer, on a competitive basis, a limited number of short-term traineeships, to be added as supplements to active NINCDS Institutional NRSA's. These awards are available to students enrolled in schools of medicine, osteopathy, dentistry and veterinary medicine, and are intended to give a limited number of selected students, in "off-quarter" experiences, opportunity for involvement in research so that they might consider clinical research as a career option. This program should, in the long run, increase the size of the physician-investigator pool. Twenty-eight Institutional training programs competed successfully for these supplements in FY '83. In addition, within the NINCDS Training Grant Program funds are being provided for 55 predoctoral, 232 postdoctoral and 150 short-term trainees in special summer programs.

National Research Service Awards for Individual Postdoctoral Fellows (Fellowships)

From FY '83 funds, the Institute provided continuation support for 93 fellows and made 97 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 fourth year of operation. The Institute made four awards totalling $99,000 during FY '83. 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	15	$ 281	18	$ 326	33	$ 607
Convulsive, Developmental & Neuromuscular Disorders	17	326	12	228	29	554
Demyelinating, Atrophic & Dementing Disorders	9	172	4	61	13	233
Fundamental Neurosciences	83	1,512	53	955	136	2,467
Stroke and Trauma	10	184	6	114	16	298
Total	134	$2,475	93	$1,684	227	$4,159

*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	$ 40	8	$ 309	9	$ 349
Convulsive, Developmental & Neuromuscular Disorders	2	82	11	392	13	474
Demyelinating, Atrophic & Dementing Disorders	0	0	7	271	7	271
Fundamental Neurosciences	6	233	18	703	24	936
Stroke and Trauma	2	81	3	118	5	199
Total	11	$436	47	$1,793	58	$2,229

*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	$ 129	17	$ 739	20	$ 868
Convulsive, Developmental & Neuromuscular Disorders	6	268	23	951	29	1,219
Demyelinating, Atrophic & Dementing Disorders	15	659	27	1,159	42	1,818
Fundamental Neurosciences	0	0	0	0	0	0
Stroke and Trauma	6	259	20	869	26	1,128
Total	30	$1,315	87	$3,718	117	$5,033

*Amounts in thousands

Annual Report
October 1, 1982 through September 30, 1983
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. The Grants Administration Section is responsible for the administrative management of the NINCDS' five extramural grant Programs. These grant programs are funded through a variety of mechanisms, i.e., research project grants, program project grants, specialized center grants, training grants, fellowship grants and career development awards. In addition, the Grants Administration Section is responsible for coordinating NINCDS responses to Freedom of Information requests. The Grants Processing Section is responsible for processing the grant applications and issuing the awards for the research, training, fellowship, and career development grants, for ensuring that funds are appropriately encumbered, and for preparing the materials for the Advisory Council meetings. There are 10 employees in each section of the GMB or a total of 20. This total is two less than that in FY '82. The reduced staff has been able to accommodate the workload due to efficiencies realized from increased utilization of the computer in preparing awards and in preparing for Council.

During Fiscal Year 1983 the GMB is responsible for a total grant budget in excess of $221 million, of which approximately $212 million is for research grants and $9 million is for training grants. The total represents a 6.5% increase over that for Fiscal Year 1982. Approximately 2,390 applications will be reviewed by the NANCDS Council during Fiscal Year 1983. This represents a 7.8% increase over that reviewed during Fiscal Year 1982.

During Fiscal Year 1983 the GMB began utilizing the computer to identify potential overlap between the support investigators receive from program projects and that they receive from other assistance and contract mechanisms at NIH. This enables the NINCDS to use its funds more efficiently and thereby support additional research.

The Grants Management Branch is responsible for coordinating responses to all Freedom of Information (FOI) requests submitted to the NINCDS. During FY '83 the GMB will process an estimated 105 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 are made for privacy purposes and patent issues are resolved.

ANNUAL REPORT
October 1, 1982, through September 30, 1983
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, five specialists, and three supporting staff.

During fiscal year 1983, the CMB was responsible for some 85 contracts and interagency agreements, totaling $13.4 million in awards. The total value of these contracts, including amounts obligated to-date, is nearly $60 million. There are 13 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 85 research contracts that have expired and are in the process of being administratively closed out.

During fiscal year 1983, the CMB issued 23 Request for Proposals (RFPs) for the purpose of soliciting new contract projects, renewing some, and recompeting several ongoing projects. It is expected that approximately 19 new contract awards will be made during the year. Added to this workload are 50 renewals of existing contracts with additional funding and over 60 other actions modifying contracts in some manner but not requiring additional funding.

This year saw the application of a second utilization of the Master Agreement. The Master Agreement mechanism was implemented to add flexibility to the Program areas and to speed the procurement process. By the end of FY 1982, 15 Master Agreements for the Stroke Program were awarded, and 4 new contracts are expected to result from these Agreements in FY 1983. The use of the Master Agreement in the Epilepsy Program is working well and appears to be serving the purpose for which it was designed.

ANNUAL REPORT
October 1, 1982, through September 30, 1983
Administrative Services Branch
Extramural Activities Program
National Institute of Neurological and Communicative
Disorders and Stroke

The Administrative Services Branch (ASB) was established during Fiscal Year 1982 and has as its primary responsibility advising the Director, Extramural Activities Program, Program Directors and Office Chiefs of NINCDS extramural programs on matters relating to the general management and administration of the Institute's extramural programs. Advice and assistance is provided in the areas of budget formulation and execution, personnel administration, space management, procurement, travel, reproduction, and other support services.

The Branch consists of the Chief, a program analyst, three (3) administrative officers, seven (7) permanent full-time clerical support employees and three (3) stay-in-school employees.

During Fiscal Year 1983, Branch staff provided assistance in the abolition of the Neurological Disorders Program and the creation of two (2) new NINCDS extramural programs: Demyelinating, Atrophic and Dementing Disorders Program and Convulsive, Developmental and Neuromuscular Disorders Program. Branch staff also played a major role in assigning and renovating space to house staff of the new extramural programs, as well as, identifying and making recommendations to Institute management to acommodate the space needs of the existing extramural programs.

During Fiscal Year 1983, Branch staff has played a key role in recruitment, selection, and placement efforts to fill key positions in the extramural programs. Most notable among these actions are the appointment of Dr. Donald Luecke as Deputy Director, EAP who was reassigned from the Stroke and Trauma Program (STP) and Dr. George N. Eaves as Deputy Director, STP who was reassigned from the National Heart, Lung, and Blood Institute. The staff is currently involved in preparing the necessary paperwork to recruit to fill the positions of Director, DADDP and Deputy Director, CDNDP.

Two members of the staff received Quality Step Increases during FY'83 for sustained superior performance: Ms. Andrea Keyes and Ms. Jeannie Giddings. One employee received a Cash Award for a special act or service: Mr. Gary Mayo.

ANNUAL REPORT
October 1, 1982 through September 30, 1983
Scientific Review Branch
Extramural Activities Program
National Institute of Neurological
and Communicative Disorders and Stroke

The Scientific Review Branch 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, a number of ad hoc committees are convened 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, 1983 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
Eileen Pierpoint, 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 GRANT APPLICATIONS REVIEWED AND SITE VISITS MADE BY

SCIENTIFIC REVIEW BRANCH PERSONNEL ACCORDING TO TYPE OF APPLICATION

Type of Application	Number of Applications	Number of Site Visits
Program Project (P01)	68	49
Specialized Center (P50)	24	14
Cooperative Clinical Research Grant (R01)	5	4
Conference Grant (R13)	15	0
Teacher-Investigator Development Award (K07)	43	0
Institutional National Research Service Award (T32)		
New and Renewal	24	0
Supplemental	34	0
TOTAL	213	67

The table shows that 213 grant applications were reviewed and that 67 site visits were made. It should be noted that 34 of the applications were supplemental applications submitted by NRSA training grant awardees who were interested in support for the short term training of students in professional schools. It is also important to note that the number of applications and number of site visits for applications going to the January 1984 Council has been estimated.

Concerning the technical merit review of contract proposals, 76 were received in response to 23 RFPs, seven of which did not require a technical merit review. Responses are due for an additional RFP 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 in order to identify the most qualified individuals to serve on our technical merit review committees and *ad hoc* panels.

TAB 3 -- COMMUNICATIVE DISORDERS PROGRAM -- CDP

ANNUAL REPORT
October 1, 1982 through September 30, 1983
Communicative Disorders Program
National Institute of Neurological and
Communicative Disorders and Stroke

TABLE OF CONTENTS

ANNUAL REPORT
October 1, 1982 through September 30, 1983
Communicative Disorders Program
National Institute of Neurological and
Communicative Disorders and Stroke

Introduction

Through the medium of research grants, contracts and training fellowships, the Communicative Disorders Program addresses the function and disorders of the communicative senses including hearing, language, speech, taste and smell. Individuals with hearing disorders alone comprise one of the largest groups of handicapped persons; hearing studies initiated or completed during the year have focused on the causes of hearing impairment, improved hearing aids and presbycusis (the hearing impairment commonly associated with aging). Language impairment in the preschool years creates a barrier which precludes the normal development of speaking, reading and writing skills; studies completed during the year have resulted in improved instruments for the measurement of language acquisition potential and for the identification of preschool children at risk for impaired language skills. The senses of taste and smell, the "chemosenses", have been described as the "special senses"; however, studies completed during the year have demonstrated that taste and smell may play a central role in modulating human behavior.

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, and was appointed Acting Associate Director of Communicative Disorders for the Institute.

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 Nadine Connor, M.A., 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.

Communicative Disorders Program Activities

Advisory Committee Meeting

The Scientific Program Advisory Committee (Communicative Disorders) met on Monday, May 2, 1983. The following Advisors were present:

Dr. Robert C. Bilger
University of Illinois

Dr. Sheila E. Blumstein
Brown University

Dr. Norman Geschwind (ad hoc)
Beth Israel Hospital

Dr. Ernest Mhoon
University of Chicago

Dr. Murray B. Sachs (ad hoc)
Johns Hopkins School of Medicine

Dr. David V. Smith
University of Wyoming

Program staff also attended this meeting. The Advisors have provided direction to the Program concerning 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 them or suggesting modifications.

Presentations at Professional Meetings and Scientific Societies

Connor N. "Refining the Voiced-Voiceless Distinction in Esophageal Speech with Biofeedback." American Speech-Language-Hearing Association..

Elkins E. "Behavioral Characteristics of the Deaf and Hard-of-Hearing Infant and Child." Johns Hopkins University.

Ludlow CL. "Objective measures for assessing speech impairments in dysarthria and treatment design." Canadian Speech and Hearing Association.

Ludlow CL, Bassich CJ, Coulter DC. "The relationship between frequency perturbation and ratings of vocal quality." American Speech-Language-Hearing Association.

Ludlow CL, Connor N, Coulter DC. "Preliminary results evaluating the concept of an optimum phonatory frequency in normal and pathological speakers." The Voice Foundation 12th Annual Symposium: Care of the Professional Voice.

Ludlow CL, Coulter DC, Connor N, Gentges FH. "Identification of phonatory measures reflective of changes in vocal fold morphology." Association for Research in Otolaryngology.

Ludlow CL, Naunton RF, Bassich CJ. "Prediction of the outcome of recurrent laryngeal section in the treatment of spastic dysphonia." American Academy of Otolaryngology - Head and Neck Surgery.

Ludlow CL, Rosenberg J, Dillon D, Buck D. "Persistent speech dysprosody following penetrating head injuries." American Speech-Language-Hearing Association.

Ludlow CL, Rosenberg J, Fair C, Buck D, Dillon D. "Comparison of brain lesions associated with and without recovery from expressive aphasia." Academy of Aphasia.

Moore EJ, Counter A, Gardi J, Hashimoto I, Moller A. "Generators of auditory brainstem evoked responses." American Speech-Language-Hearing Association Conference.

Moore EJ. Eminent Scholar Lecture: "Introduction to the National Institutes of Health." Norfolk State University.

Naunton RF. "Research in otolaryngology." Society of University Otolaryngologists.

Naunton RF, Moore EJ. "How to prepare an NIH research grant application." American Academy of Otolaryngology - Head and Neck Surgery.

Naunton RF. "Audiograms." Walter Reed Army Hospital Medical Center.

Naunton RF. "New NIH initiatives." Colorado Otology-Audiology Conference.

Pearl J. "Chemosensory Research Support: National Institute of Neurological and Communicative Disorders and Stroke." Association for Chemoreception Sciences.

Pearl J. "The Chemosenses: A Review of the State of Basic Science and Clinical Aspects of Olfaction and Gustation." Association for Research in Otolaryngology.

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

Honors and Awards

Dr. Ludlow:

- Elected a Fellow of the American Speech-Language-Hearing Association in November 1982 in recognition of her outstanding scientific achievements in speech and language research, her contributions to the Association and her administrative accomplishments.

Dr. Moore:

- Named "Eminent Scholar Lecturer" by Norfolk State University, in March of 1983, in recognition of his outstanding scientific accomplishments.

Other Staff Activities

Dr. Elkins:

- Conducted a national workshop at NIH on the topic "Speech recognition for the hearing impaired."
- Served on a planning committee concerning the Veterans Administration evaluation of hearing aids and assistive devices for the deaf.
- Participated in a program planning meeting with Self Help for the Hard of Hearing (Shhh).
- Participated in a planning committee for the Fall 1983 scientific symposium of the Committee on Hearing, Biomechanics and Bioacoustics (CHABA).

Dr. Ludlow:

- Served on Scientific Affairs Committee of the American Speech-Language-Hearing Association.
- Served on Information Task Force, American Speech-Language-Hearing Association.
- Served on Speech Communication Technical Committee, Acoustical Society of America.
- Served on Consortium of Affiliates for International Programs of the American Association for the Advancement of Science.
- Served as consultant in speech and language research, Vietnam Head Injury Study, Walter Reed Army Medical Center.
- Served as chairman, Journal Selection Committee, Deafness, Speech and Hearing Abstracts.
- Served on Editorial Advisory Board, Journal of Developmental and Behavioral Pediatrics.
- Served as Associate Editor, (Neuropathologies) Journal of Speech and Hearing Research.

Dr. Moore:

- Represented Program at annual meeting of the National Black Association, for Speech, Language and Hearing (NBASLH).
- Served as chairman, Scientific Exhibits Committee, American Speech-Language-Hearing Association.

Dr. Naunton:

- Served as chairman, Membership and Credentials Committee, American Neurotology Society.
- Served as member, Editorial 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.
- Served as otologic consultant to Walter Reed Army Hospital Medical Center.
- Interviewed on television (Channel 9) on "Motion Sickness."
- Interviewed on CBS radio on "Hearing Impairment."
- Presented luncheon address "Health Care Initiatives for the 80's." Better Hearing and Speech Month opening ceremony.
- Interviewed by U.S. News and World Reports, - "Hearing Impairment."

Dr. Pearl:

- Served as Institute representative at the Conference on Human Taste and Smell, Measurement and Uses; Memorial Sloan-Kettering Cancer Center.
- Served as member, NINCDS Equal Employment Opportunity advisory committee.
- Served as Program representative, NINCDS Symposium on Pain Measurement and Assessment.

Dr. Ranney:

- Appointed member of the Deafness/Hearing Impairment Interagency Committee organized by the National Institute of Handicapped Research.
- Represented the Program at the Self Help for the Hard of Hearing (Shhh) Open House.

Dr. Reiner:

- Served as Associate Editor, dsh Abstracts.
- Served as consultant to Maryland Speech-Language-Hearing Association on survey design.

Clinical Activities

Dr. Elkins

Clinical research in hearing impairment is a collaborative endeavor with the Audiology Service of the Clinical Center in which Dr. Elkins provides direction, experimental design and analyses for fifteen studies. Ms. Pikus, Chief Audiologist, with Ms. Grimes and Ms. Vernon, have developed liaisons with other Institutes, to conduct the following studies of hearing impairment associated with various diseases and disorders: identification of carrier status in selected genetic diseases; ototoxicity as related to chemotherapeutic agents and radiation; hearing status of patients with selected neurological disorders; and a profile of risk factors for presbycusis. Results of the study on Central Neurofibromatosis indicate that acoustic reflex and auditory brain stem response measures appear to be sensitive indices in the early detection of acoustic neuroma and suggest that either or both measures are likely to identify tumors that are below the resolution ability of CAT scanning. Preliminary data also suggest the usefulness of the auditory brain stem measures as a management tool for documenting the progress of the disease. The study on autism with 25 experimental and 25 control subjects, suggests that autistic patients do not evidence abnormal auditory brain stem responses except for variable (some prolonged and some shortened) Wave I and III intervals. Details of other studies in progress may be found in the research project reports.

Dr. Ludlow

The clinical speech and language research program conducts studies of patients with phonatory and speech motor disorders (dysarthrias) secondary to neurologic disease. The goal of the research is to identify separate components of speech and phonatory control and their neurologic organization through the analysis of patterns of speech breakdown in different forms of neurologic disease. Studies manipulating the rate of patients' speech are aimed at determining how speech movement velocity and inter-articulator coordination and timing are affected in different neuropathologies. Studies of phonatory functioning in patients with neurological abnormalities and morphologic pathologies of the larynx are aimed at determining how phonatory vibration is altered by changes in neural control at different levels of the CNS and how such alterations differ from the effects of structural changes in the larynx.

At present, seven areas of study are ongoing:

1. Acoustic studies of patterns of vocal fold vibration in phonatory pathology.

2. Investigation of the validity of the concept of optimum frequency in normal and pathological phonation.

3. Studies of the characteristics of voice disorders of unknown etiology (Spastic Dysphonia and Vocal Tremor).

4. Analysis of speech timing disorders resulting from neuropathologies at different levels of the CNS.

5. Effects of experimental rate manipulation on speech movement and timing control in different forms of CNS Disease.

6. Relationships between language and speech production deficits on subcortical neuropathologies.

7. The relationship between the location and size of brain lesions and speech motor control deficits subsequent to penetrating head injuries.

Highlights of this program during the past year are as follows:

Patterns of Vocal Fold Vibration in Different Forms of Laryngeal Pathology

To determine how particular types of laryngeal abnormalities affect phonatory vibration, our approach has been to select groups of patients with well defined neurologic or morphologic pathologies affecting phonation and compare the results of acoustic analyses of the vibratory pattern both with normal subjects and between patient groups. Thus far, two groups of patients have been studied: patients with laryngeal nodules and polyps; and patients with Parkinson's disease and increased vocal fold tension as evidence by their higher fundamental voice frequency. In comparison with normals, patients with vocal fold nodules and polyps had increased frequency perturbation and no significant differences from normals in amplitude perturbation. In contrast, Parkinson patients showed no increase in frequency perturbation in comparison with normals but had significantly greater amplitude perturbation and linear trend in amplitude. Thus far, these studies indicate the differential effects of morphologic and neurologic alterations on the resulting acoustic signal. Mass changes due to neoplastic pathologies alter the stability of the period length, while tension changes in neurologic pathologies affect the stability of period amplitude.

Validity of the Concept of an Optimum Frequency of Phonatory Functions

The aim of these studies is to determine how phonatory functioning changes in normalcy and pathology at different fundamental frequencies in order to determine the validity of the concept of optimum pitch. This concept predicts that the ease of phonation, acoustic power and stability of vibration is greatest in a particular frequency range for each individual. This concept has served as the basis of treatment for many types of vocal pathology.

Three groups of patients are being evaluated in studies comparing phonatory functioning (maximum duration per air volume, acoustic power, and stability of vibration) at three frequencies, optimum pitch, a selected pitch level and higher pitch level. Thus far the results indicate that phonatory functioning improves with increasing frequency in normal speakers. This does not hold in various types of pathology. In vocal fold nodules and polyps, vibratory stability was improved at low frequencies while in unilateral vocal fold paralysis the acoustic power of phonation and vibratory stability were greater at the low and middle range phonatory frequencies respectively.

Characteristics of Spastic Dysphonia

Spastic dysphonia is a specific phonatory disorder of unknown etiology; some patients are benefited by unilateral section of the recurrent laryngeal nerve. A study was completed aimed at identifying whether phonatory characteristics could

differentiate between patients who will benefit from surgery and those who will not. Laryngeal movement was videotaped during respiration, phonation, and speech, and signs of different laryngeal movement disorders were identified; these differentiated between those benefiting from temporary nerve block and subsequent surgical section and those not benefiting from a temporary block. The latter group had phonatory characteristics more typical of vocal tremor and were benefited by alterations in auditory feedback while the vocal symptoms of those patients more typical of spastic dysphonia were marked by spasms with excessive supralaryngeal constrictions of the vocal tract.

Patterns of Speech Timing Disorders in Different Neuropathologies

Different groups of patients were compared on measures of speech timing at the suprasegmental and segmental levels. It was found that patients with Parkinson's disease and hypokinesia were not only affected in their overall speech rate at the suprasegmental level, but that coordination and timing between articulator movement onsets were impaired at the segmental level, suggesting the presence of a motor programming disorder in Parkinson's disease and not just a rate disorder. In contrast, the overall rate at both the suprasegmental and segmental levels was impaired in Huntington's disease although as yet no evidence has been found of a speech motor programming disorder.

New studies have been initiated in this area using instrumentation which transduces the displacement of the rib cage and abdomen, and the displacement and velocity of the lip and jaw during speech production. This allows for a more direct study of the timing pattern of the coordination of articulator movement onsets and offsets during speech in different forms of neurologic disease.

Effects of Rate Manipulation on Speech Movement Velocity

The effects of manipulating speech rate in patients with cerebellar disease and with dystonia were compared. Cerebellar disease was found to limit the ability of patients to intrinsically alter their own speech and movement velocity. However, the pattern of interarticulation coordination remained intact in these patients. Patients with dystonia were able to intrinsically alter both their speech rate and movement velocity but the pattern of interarticulator coordination was abnormal, particularly at slow speech rates, suggesting a motor programming disorder in dystonia but not in cerebellar pathology.

Relationship Between Language and Speech Deficits in Subcortical Neuropathologies

Patients with hypokinetic Parkinson's disease were examined for a language processing disorder in comparison with age and sex matched controls. Significant expressive and receptive language deficits were found in the Parkinson patients, with impaired sentence comprehension. These deficits were related to patients' abilities to retrieve previously learned information on tests of memory but not short term memory or new learning abilities. The language deficits were only significantly related to the patients' latencies of speech initiation, indicating that these patients have less efficient language processing for both expression and reception which was related to their speed of response on speech tasks.

Location and Size of Brain Lesions Associated with Speech Motor Control Deficits

Ten patients were found presenting a syndrome of speech dysprosody similar to the rate disorder previously reported as associated with post-encephalitic Parkinson's disease. Comparison of the frequency of involvement of particular brain structures in this group with other head injured patients without speech motor control deficits, determined that this syndrome was associated with right or left sided lesions to the following structures: the pars opercularis, the anterior internal capsule, the anterior corona radiata and the neostriatum.

Dr. Moore

Dr. Moore has participated in the activities of the Surgical Neurology Branch (Paul L. Kornblith, M.D., Chief) and the Clinical Neurosciences Branch in conducting studies of various evoked electrical potentials. The purpose of a current project is to investigate the evoked potential correlates of neurologically normal individuals and of individuals with central nervous system abnormalities. A combined evoked potential paradigm is used, capitalizing on information gained from recording short- and long-latency auditory evoked potentials, short-latency somatosensory evoked potentials and long-latency visual evoked potentials.

Staff Publications

Caine ED, Polinsky RJ, Ludlow CL, Ebert MH, Nee LE. Heterogeneity and variability in Tourette's Syndrome. Advances in Neurology. 35, 437-442, 1982.

Caine ED, Ludlow CL, Polinsky RJ, Ebert MH. Provocative drug testing in Tourette Syndrome. Journal of the American Academy of Child Psychiatry. In press.

Hanson D, Ludlow CL, Bassich CJ. Vocal fold paresis in Shy-Drager syndrome. Annals of Otology, Rhinology and Laryngology. 92, 85-90, 1983.

Hinojosa R, Lindsay JR, Matz GJ, Naunton RF. The inner ear. In: Riddell RH, ed. Pathology of Drug-Induced and Toxic Diseases. New York: Churchill Livingstone, 155-166, 1982.

Ludlow CL, Polinsky RJ, Caine ED, Bassich CJ, Ebert MH. Language and speech abnormalities in Tourette's syndrome. Advances in Neurology. 35, 351-361, 1982.

Ludlow CL, Cudahy E, Bassich CJ, Brown GL. Auditory processing skills of hyperactive, reading and language impaired boys. In: Katz J, Lasky E, eds. Central Auditory Processing Disorders: Problems of Speech, Language and Learning. University Park Press, Baltimore. In press.

Ludlow CL, Coulter D, Gentges F. Differential sensitivity of frequency perturbation to laryngeal neoplasms and neuropathologies. In Abbs J, Bless D, eds. Proceedings of International Conference on Vocal Fold Physiology. College-Hill Press, San Diego. In press.

Ludlow CL, Cooper J, eds. Genetics of Speech and Language Disorders. Academic Press, New York, New York. In press.

Ludlow CL, Cooper J. Genetic aspects of speech and language disorders: Current status and future research directions. In Ludlow CL, Cooper J, eds. Genetics of Speech and Language Disorders. Academic Press, New York. In press.

Ludlow CL, Coulter D, Gentges F. The effects of change in vocal fold morphology on phonation. In: Lawrence, Van L ed. Transcripts of the 11th Annual Symposium: Care of the Professional Voice. The Voice Foundation, New York, New York. In press.

Ludlow CL. Evaluation of treatment of children with language disorders. In: Perkins WH ed. Current therapy of Communicative Disorders. Thieme-Stratton, New York, New York. In press.

Ludlow CL, Naunton RF, Bassich CJ. Procedures for selecting spastic dysphonia patients for recurrent laryngeal nerve section. Annals of Otolaryngology-Head and Neck Surgery. In press.

Ludlow CL, Bassich CJ. Relationships between perceptual ratings and acoustic measures of hypokinetic speech. In: McNeil MR, Rosenbek JC, Aronson AE eds. Dysarthria and Apraxia of Speech: Physiology-Acoustics-Linguistics-Management. College-Hill Press, San Diego, California. In press.

Ludlow CL, Bassich CJ. The results of acoustic and perceptual assessment of two types of dysarthria. In: Berry W, ed. Clinical Dysarthria, San Diego, California, College-Hill Press, 121-154.

Ludlow CL. The brain bases for language functioning: New insights from penetrating head injuries. In: Byrnes H, ed. Proceedings of Conference on Contemporary Perceptions of Language: Interdisciplinary Dimensions, Washington, D.C., Georgetown University Press, 203-223, 1983.

Ludlow CL. Identification and assessment of aphasic patients for language intervention. In: Miller J, Yoder DE, Schiefelbusch R, eds. Language Intervention, Trenton, New Jersey, B. C. Decker, Inc., 75-91, 1983.

Moore EJ, ed. Bases of Auditory Brain Stem Evoked Responses. Grune and Stratton, Inc., New York, 1983.

Moore EJ. History of BSER. In: Moore EJ, ed. Bases of Auditory Brain Stem Evoked Responses. Grune and Stratton, Inc., New York, 1983.

Moore EJ. Effects of Stimulus Parameters on BSER. In: Moore EJ, ed. Bases of Auditory Brain Stem Evoked Responses. Grune and Stratton, Inc., New York, 1983.

Naunton RF. NIH and otolaryngology: a promising partnership. Ear Nose Throat J. 61:531-535, 1982.

Naunton RF. NIH research programs: communicative disorders. Osteopathic Ann. 10:565-571, 1982.

Naunton RF. Clinical research in the health sciences: a collaborative venture. Corti's Organ. 6(2):1, 1981.

Staff Publications

Caine ED, Polinsky RJ, Ludlow CL, Ebert MH, Nee LE. Heterogeneity and variability in Tourette's Syndrome. Advances in Neurology. 35, 437-442, 1982.

Caine ED, Ludlow CL, Polinsky RJ, Ebert MH. Provocative drug testing in Tourette Syndrome. Journal of the American Academy of Child Psychiatry. In press.

Hanson D, Ludlow CL, Bassich CJ. Vocal fold paresis in Shy-Drager syndrome. Annals of Otology, Rhinology and Laryngology. 92, 85-90, 1983.

Hinojosa R, Lindsay JR, Matz GJ, Naunton RF. The inner ear. In: Riddell RH, ed. Pathology of Drug-Induced and Toxic Diseases. New York: Churchill Livingstone, 155-166, 1982.

Ludlow CL, Polinsky RJ, Caine ED, Bassich CJ, Ebert MH. Language and speech abnormalities in Tourette's syndrome. Advances in Neurology. 35, 351-361, 1982.

Ludlow CL, Cudahy E, Bassich CJ, Brown GL. Auditory processing skills of hyperactive, reading and language impaired boys. In: Katz J, Lasky E, eds. Central Auditory Processing Disorders: Problems of Speech, Language and Learning. University Park Press, Baltimore. In press.

Ludlow CL, Coulter D, Gentges F. Differential sensitivity of frequency perturbation to laryngeal neoplasms and neuropathologies. In Abbs J, Bless D, eds. Proceedings of International Conference on Vocal Fold Physiology. College-Hill Press, San Diego. In press.

Ludlow CL, Cooper J, eds. Genetics of Speech and Language Disorders. Academic Press, New York, New York. In press.

Ludlow CL, Cooper J. Genetic aspects of speech and language disorders: Current status and future research directions. In Ludlow CL, Cooper J, eds. Genetics of Speech and Language Disorders. Academic Press, New York. In press.

Ludlow CL, Coulter D, Gentges F. The effects of change in vocal fold morphology on phonation. In: Lawrence, Van L ed. Transcripts of the 11th Annual Symposium: Care of the Professional Voice. The Voice Foundation, New York, New York. In press.

Ludlow CL. Evaluation of treatment of children with language disorders. In: Perkins WH ed. Current therapy of Communicative Disorders. Thieme-Stratton, New York, New York. In press.

Ludlow CL, Naunton RF, Bassich CJ. Procedures for selecting spastic dysphonia patients for recurrent laryngeal nerve section. Annals of Otolaryngology-Head and Neck Surgery. In press.

Ludlow CL, Bassich CJ. Relationships between perceptual ratings and acoustic measures of hypokinetic speech. In: McNeil MR, Rosenbek JC, Aronson AE eds. Dysarthria and Apraxia of Speech: Physiology-Acoustics-Linguistics-Management. College-Hill Press, San Diego, California. In press.

Ludlow CL, Bassich CJ. The results of acoustic and perceptual assessment of two types of dysarthria. In: Berry W, ed. Clinical Dysarthria, San Diego, California, College-Hill Press, 121-154.

Ludlow CL. The brain bases for language functioning: New insights from penetrating head injuries. In: Byrnes H, ed. Proceedings of Conference on Contemporary Perceptions of Language: Interdisciplinary Dimensions, Washington, D.C., Georgetown University Press, 203-223, 1983.

Ludlow CL. Identification and assessment of aphasic patients for language intervention. In: Miller J, Yoder DE, Schiefelbusch R, eds. Language Intervention, Trenton, New Jersey, B. C. Decker, Inc., 75-91, 1983.

Moore EJ, ed. Bases of Auditory Brain Stem Evoked Responses. Grune and Stratton, Inc., New York, 1983.

Moore EJ. History of BSER. In: Moore EJ, ed. Bases of Auditory Brain Stem Evoked Responses. Grune and Stratton, Inc., New York, 1983.

Moore EJ. Effects of Stimulus Parameters on BSER. In: Moore EJ, ed. Bases of Auditory Brain Stem Evoked Responses. Grune and Stratton, Inc., New York, 1983.

Naunton RF. NIH and otolaryngology: a promising partnership. Ear Nose Throat J. 61:531-535, 1982.

Naunton RF. NIH research programs: communicative disorders. Osteopathic Ann. 10:565-571, 1982.

Naunton RF. Clinical research in the health sciences: a collaborative venture. Corti's Organ. 6(2):1, 1981.

The Cochleo-Vestibular System: Biological Basis

Auditory Deprivation

Early findings indicate that peripheral hearing losses (even those considered mild to moderate) are directly related to anatomical changes in morphology. Animal studies have shown that lack of auditory stimulation at different stages of development tends to retard normal development of the central auditory nervous system. If auditory deprivation leads to severe dystrophies in the auditory system, the earlier these deprivations can be identified and appropriate stimulation provided, the more neural elements might be preserved. Implications for new habilitative techniques are apparent; current methods for activating portions of the central nervous system to establish language and other cognitive functions should be reevaluated. Normal development may not be the model for habilitating the child with an impaired peripheral/central auditory system.

Cochlear Mechanics

Laser interferometry and the Mossbauer technique are two new tools now being used in studies of the mechanical properties of the cochlea. They promise to elucidate such questions concerning basilar membrane motion as its linearity, and whether its frequency-dependency resembles that of the auditory nerve-fiber output or is dependent on the mechanical properties of other cochlear structures.

Ototoxicity

Studies of the mechanisms of ototoxicity have reemphasized the reversibility of aspirin ototoxicity. The mechanism of this reversal remains obscure, as does the ear's recovery from temporary threshold shifts. Further studies of these relationships may lead to therapeutic intervention in the prevention or treatment of some varieties of hearing impairment.

Stimulus-Related DC Potentials of the Cochlea

Efforts continue to quantify the various DC electrical potentials that can be recorded from the mammalian cochlea in response to sound stimulation. These DC potentials are an aggregate response, composed of several components, all of which presumably originate at different sites and have their genesis in different mechanisms within the cochlea. The purpose is to identify these mechanisms and sources, and to delineate the significance of these DC components in the hearing process. Investigators have recorded and identified the post-synaptic potentials of the cochlea, hypothesized to be the direct precursors of all-or-none discharges in the auditory nerve. They have also investigated the properties of the compound action potential of the auditory nerve, and correlated changes in this response with experimentally-induced cochlear pathology.

Cochlear Afferent Transmitters

Work continues in an effort to identify the primary afferent sensory transmitters and their associated biochemical systems. The lateral-line hair cells of Zenopus laevis (The African clawed frog) and of the inner ear hair cells of the guinea pig serve as experimental specimens. Transmitter-like materials released into perilymph during exposure of guinea pigs to noise at high levels have been identified. Major techniques include: (1) high-performance liquid chromatography with fluorescence detection of primary amines for the analysis of perilymph, (2) one- and two-dimensional gel electrophoresis for detection of proteins specific to hair-cell fractions, and (3) radioactive receptor binding assays for the determination of neurotransmitter-binding sites in the lateral-line sensory epithelium.

Neural Regeneration in the Auditory System

Previous studies have revealed that hair cell production of the inner ear sensory epithelia of sharks and rays continues through the post-embryonic stages and that this results in a vast increase in physiologic sensitivity. The perpetual growth of labyrinthine receptor organs among fishes, and at least to maturity among amphibians, is apparently similar to inner ear maturation during the embryonic stages of mammals where hair cell production does not continue after birth. Several experiments have revealed information concerning the origins and locations of new hair cells, the mechanisms by which these new cells are innervated, and the physiologic correlates that accompany the increase in numbers of hair cells and nerve terminals.

Recent studies have also revealed that these sensory epithelia are heterogeneous. There are structural differences in the hair cells located in different regions of the receptor epithelium which reflect different physiologic characteristics. Radioactive mitotic labeling, and microautoradiographic localization methods have assisted in determining the origin, and number of hair cells during post-embryonic growth within the saccule of giant neotropical toads.

The Cochleo-Vestibular System: Clinical Studies

Cholesteatoma

Investigators have successfully established a guinea pig model of middle ear cholesteatoma which now permits studies of cholesteatoma development using morphologic and immunocytochemical techniques. A specific collagenolytic enzyme has been localized and quantified. Additionally, the role of inflammatory connective tissue and epithelium migration in collagen degradation and decalcification has been studied biochemically using inflammation-induced granulomas. This animal bone resorption model continues to prove valuable in the assessment of factors producing middle ear cholesteatoma in the human.

Human Temporal Bone Pathology

The study of well documented human temporal bones has yielded a great deal of information concerning the histopathologic bases of many varieties of hearing impairment. This work continues, with the addition of ultra-microscopic studies.

Cochleo-Vestibular Ototoxicity

The effects of ototoxic aminoglycoside antibiotics on the dynamics of the human vestibulo-ocular and vestibulo-spinal reflex systems, and the adaptive properties of these reflexes following total loss of vestibular function have been evaluated. These studies were performed in patients receiving aminoglycoside antibiotics by testing them with various combinations of oculomotor pursuit, optokinetic and rotational vestibular stimuli. Upright postural control was studied by manipulation of visual and ankle joint proprioception in patients with aminoglycoside-induced vestibular ototoxicity. The results of these studies are advancing the health care of patients receiving ototoxic antibiotics by providing sensitive quantitative methods for early detection of vestibular aminoglycoside ototoxity; they are providing incidence figures for commonly used aminoglycoside antibiotics and are contributing information about adaptive motor reflex mechanisms in individual patients.

Microcomputer-Based Instrumentation for Vestibular Function Testing

The overall goal of this work has been to demonstrate the utility of a stand-alone device in improving accuracy, reducing labor, and standardizing the procedures for vestibular function tests. A prototype instrument has been assembled. One microprocessor instrument collects and analyzes nystagmus data recorded via electro-oculography and presents summary information to the operator. A second microprocessor controls the generation of several vestibular stimuli including a moving chair optokinetic device and caloric stimulator. Clinical evaluation of the nystagus analyzer has demonstrated the accuracy and reliability of the computer analysis of eye movements and the degree of acceptance of the device by clinical users. As an aid in the evaluation process, work was completed on a digitized manually annotated data base of a spectrum of vestibular and oculomotor responses, both normal and abnormal. Computer analysis has now been compared to the manual reading via a comparator program. The computer analysis algorithms are adjusted for optimum human performance.

Noise-Induced Hearing Loss (NIHL)

The damaging effects of continuous noise are fairly well understood but studies are only now beginning on the effects of exposure to intermittent noise. As a result, there needs to be a reevaluation of the "safe" level of noise exposure over time. Some current work questions whether 90 dBA is too lenient for continuous noise-exposure. Certain drugs have been shown to reduce the mechanical effect of noise trauma; this may be an indication that the mechanism of NIHL is not only mechanical but also biochemical and/or metabolic.

Otitis Media with Effusion (OME)

Otitis media with effusion is a common condition in children and frequently leads to hearing impairment at a critical stage of development. Current work is clarifying the role of sub-clinical infections in OME pathogenesis and the role of the immune response in the formation of effusions.

Animal models of OME have also been developed. Many cases of OME are low-grade infections modified by the bacteriostatic substances in the effusion; the

infecting organisms develop a tolerance to these substances. Inadequate antibiotic treatment of an initial ear infection may impede the development of adequate immunity of the ear, particularly in the young age group with immature immune systems; subsequent middle ear infection results in OME.

Masking Level Differences (MLD)

Psychophysical studies of the MLD phenomenon, and current clinical data derived from auditory evoked potentials of the brainstem, permit detection of lesions of the brainstem nuclei. Early findings indicate that patients with central nervous system lesions show reduced or absent MLDs. This work may have implications for differentiating the age component of hearing impairment from more peripheral damage such as results from drug and noise damage.

Real-time Acoustic Processing

Real-time acoustic processing has been incorporated in computer-simulated transmission systems. A wearable digital hearing aid incorporating similar acoustic processing techniques will be developed in the forseeable future; such an instrument could be programmed to match the hearing characteristics of individual hearing impaired subjects.

Psychophysical Studies of Cochlear Implant Patients

Data concerning deaf patients who have received implanted cochlear prostheses is accumulating. Studies have assessed patients' abilities to perceive a brief interruption, or gap, in the cochlear electrical signal. The gap-detection paradigm is designed to provide a measure of the time course of decay in the auditory sensation that persists from stimulation. Data is provided on the range of auditory performance in a relatively large group of implant patients who have all had experience using the same type of auditory prosthesis. These findings have contributed importantly to the baseline auditory data needed for development of a more effective auditory prosthesis for the profoundly deaf.

Speech and Language: Biological Basis

Cortical Representation of Muscle Action

Microstimulation studies of the cortical representation of the lip, jaw, tongue, and laryngeal muscles in chimpanzees have demonstrated that different muscles are represented less topographically than was previously thought, and that patterns of muscular contraction can be elicited from single cell stimulation. The discovery of these cells controlling coordination among several muscles, may provide a basic understanding of how complex speech movements could develop in man.

Speech and Language: Clinical Studies

The National X-ray Microbeam Center for Speech Research

In 1980, the Communicative Disorders Program initiated the development of an X-ray Microbeam Center as a national resource for the study of speech production. In the first two years, engineers made significant advances in developing a

unique system which will allow the study of tongue movements without disturbance of speech. Previously it was not possible to study tongue movements without risk of x-ray exposure and without disturbance of the speech mechanism. Since the tongue is the major speech articulator, it is expected that development of this facility will significantly advance the field of speech research. The system will be available for use by late 1984.

A New Language Training Approach for Infantile Autism

A recent study of language training in children with infantile autism compared four methods of training: sign only, speech only, speech and sign combined and speech and sign alternating. Speech and sign alternating was found to be the most effective method, particularly for speech training in the non-echolalic subjects. Total communication training, using speech and sign simultaneously, was not as effective as the alternating method in which subjects received training in speech and sign independently. These results indicate that autistic children cannot spontaneously transfer language information from one modality to another but that learning sign enhances language and speech development in these children.

Preschool Language Screening Tool

A new test for screening for speech and language disorders in preschoolers between three and four years of age has recently been published; this was developed under an NINCDS contract. Validated test forms are available for screening Anglo and Black dialect children for speech and language disorders. Recent studies of 3-1/2 year olds found that over 14% exhibit some delay in developmental language which is moderate to severe in 10% and requires treatment. The NINCDS is providing a copy of the screening test to all state departments of early education and public health for their use in preschool screening for developmental disorders.

Speech Prostheses for Non-Vocal Patients

Rapid technological advances in microprocessors and speech synthesizers are now providing artificial speech for the severely handicapped. Patients in the terminal stages of many neurological diseases have previously been "locked in" by their inability to speak at the time they most needed to communicate. Now microcomputers can speak and write messages for such patients in response to their slightest movements such as blowing through a straw, etc. Similarly, severely handicapped cerebral palsied children are now being educated by means of talking microcomputers; they operate them with head pointers or joy sticks, the computer speaking their answers in the classroom for them. Investigators are now constructing devices which will enable the severely physically disabled to use eye movements to control speech synthesizers.

Due to the rapid development of devices for non-vocal patients, the prescription of such devices has become exceedingly complex. They are costly and the ability of a patient to operate different input devices must be predicted from assessment of such residual motor capabilities, as sucking, blowing, head movement or eye movements. A prescriptive system is now being developed that will predict the device needs of individual patients. A single microprocessor will assess patients' motor and sensory processing capabilities for operating such devices.

Brain Representation of American Sign Language in the Congenitally Deaf

Several studies have been initiated in the last year to examine the brain representation for American Sign Language (ASL) in the congenitally deaf. Because this is a manual - visually coded language, there is good reason to believe that right hemisphere representation might be greater due to the dominant role of that hemisphere in processing visuo-spatial information. One investigator is conducting electrophysiological studies of the laterality of brain responses to sign stimuli in congenitally deaf adults. Another is studying language breakdown in congenitally deaf adults whose native language is ASL and who have sustained a stroke. Studies of their residual language functioning, and CT scanning to localize brain lesions, will determine the brain representation of this language form.

This research has important theoretical implications for language representation in the brain. The brain organization underlying sign language will tell us what is left hemispheric about language dominance in that hemisphere. If sign language is represented in the left hemisphere then left hemisphere dominance would appear to be largely due to the symbolic functions of language. Such findings would also indicate that there is no pathology of the left hemisphere in the congenitally deaf. If however, sign language representation is in the right hemisphere, the visual nature of sign language may account for its localization there. Alternatively, certain forms of congenital deafness may produce abnormal left hemispheric development (due to abnormal cell migration patterns) which could account for the difficulties of the congenitally deaf in learning to read and write. If organization for language is in the right hemisphere, then the tracts required for transfer and integration of linguistic information for writing with the right hand will be quite different in the congenitally deaf than in the hearing population.

Language Recovery in Aphasia

Regional blood flow studies in aphasic patients during the early months following stroke have shown that activation of the right hemisphere for language behavior does not increase during recovery. Thus, language recovery in aphasia is independent of the transfer of language to the right hemisphere. Recovery of speech fluency has also been shown dependent upon intact structures underlying the cortex in the left hemisphere and not on the involvement of Broca's area. These findings indicate that previous theories regarding the importance of cortical regions to speech and language were incorrect and revise our understanding of the role of various brain structures in these functions. It is anticipated that further progress in this direction will permit the prediction of language recovery in aphasic patients following stroke and will contribute to our knowledge of the relation between language behavior and brain organization.

The Structural Bases of Reading, Writing and Language Disorders

The central nervous system bases of language development disorders, which impair reading and writing skills and which persist throughout life, remain obscure. Brain lesions acquired during childhood have less marked effects on language development and do not preclude the normal development of reading and writing skills. Thus, early brain lesions cannot account for developmental language disorders. Recent cytoarchitectonic studies of the brains of well documented cases of familial developmental reading disorders have shown abnormalities of

cellular organization of the left temporal lobe, in cell count and cellular organization. These findings suggest that cell migration abnormalities may have developed during fetal brain development and may be the cause of these disorders.

The Chemosenses and Touch: Biological Bases

Regeneration

The neurobiology of chemosensory neurons is serving as a model of basic membrane mechanisms. The trophic maintenance and regeneration of receptor cells is being determined. The observations that the olfactory receptor cell is the only neuron to undergo complete and continuous regeneration from precursor cells throughout the adult life of mammals and that the taste receptor cell also regenerates suggests that losses of chemosensory function in humans can be reversed. The understanding of chemosensory regeneration may be relevant to studies of regeneration in other parts of the nervous system after damage.

The effects of chemicals, axotomy, and bulbectomy on the degeneration and regeneration of the olfactory system has been further defined in biochemical, morphological, electrophysiological, and behavioral studies in animals. Only certain destructive chemicals, such as zinc sulfate, produce effects on the olfactory system. The destructive effect is not caused by a mechanical action of liquid flowing through the nasal cavity, since water and other solutions are inactive, nor by osmotic pressure, since concentrated sucrose and salt solutions are inactive, nor as a result of pH effects. Short-term exposure of the mucosa to zinc sulfate specifically affects the olfactory receptor cells. The signals produced by cell death are conveyed rapidly to nasal cells, as indicated by the rapid incorporation of ^{3}H thymidine; after prolonged exposure of the mucosa to zinc sulfate every cell type is affected and the entire tissue has to be reorganized before any olfactory cell regeneration can occur.

Common Chemical Reception

Taste and smell are separate systems with distinct receptor cells for sensing chemicals. Chemicals can also be sensed through irritation and pain by another system described as common chemical reception. Physiological responses to noxious stimuli reaching the nasal cavity include cardiovascular and pulmonary responses. The contribution of trigeminal chemoreception in the sensing of chemicals is being determined. The high degree of correlation between the magnitude of electrophysiological response of the ethmoidal nerve in rats and the perceived intensity ratings of human anosmics indicate that the rat is an excellent model for assessing the effects of odorants on human trigeminal receptors.

Blood-Born Odorants

Recent findings have indicated that odorants injected into the blood stream reach the olfactory receptors directly rather than as a result of exhalation by the lungs. This may well prove to be a precise clinical method for the measurement of olfaction.

The Chemosenses: Clinical Studies

Measurement of Taste and Smell

A readily administered test of human olfaction is now available and will facilitate the diagnosis and management of smell disorders which are associated with many medical conditions. This smell identification test consists of booklets whose pages contain tiny bubbles of odorants; the odorants are released when the subject scratches the impregnated bubbles; the test subject then attempts to identify each released odorant. For localized taste testing, pieces of filter paper, saturated with chemical solutions, are placed on the tongue.

Communication with the Deaf-Blind

Improved communication with the deaf-blind is being achieved through the presentation of vibration patterns generated by optical-to-tactile conversion instruments. Current results suggest that better reading performances can result from the static mode of presentation in which elements are presented simultaneously, rather than with a scan mode in which those same elements are presented sequentially.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1982 through September 30, 1983

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: $75,000 (forward funded)

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 tests 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: All subjects completed testing in the fall of 1983 and the team has been actively writing manuscripts from the data base. Analyses have focused on the size and location of brain lesions associated with limited recovery of particular language functions such as speech fluency, sentence comprehension and speech repetition. Patients with poor recovery of auditory comprehension had lesions in the left posterior superior temporal lobe, infrasylvian and supra-marginal regions. Those whose lesions spared these regions tended to have good recovery of auditory comprehension. Lesion volume, except when very large or very small, was not closely associated with outcome.

A study of the persistence of speech nonfluency beyond six months post onset indicated that patients with poor expressive speech had lesions in the left

lower rolandic cortical region and underlying white matter but not in Broca's area. The patients who recovered fluent speech tended to have smaller lesions and lacked extensive left rolandic lesions.

Finally, patients with speech repetition deficits persisting at six months post onset had lesions of the posterior superior left temporal lobe and not the anterior speech areas.

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 data analysis and report writing. The termination date is December 30, 1983.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1982 through September 30, 1983

PRESIDENT AND FELLOWS OF HARVARD COLLEGE, CAMBRIDGE, MASSACHUSETTS (NO1-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. 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: The research on this project was completed and the final report submitted this year. A five part research program was completed including:

(a) a review of the published literature;

(b) an analysis of data from the Third National Cancer Survey to assess the interaction of alcohol and tobacco in the incidence of laryngeal cancer;

(c) an analaysis of data from the Third National Cancer Survey to assess occupational risk factors;

(d) a case control study in the greater Augusta area in Georgia, focusing on occupational risk factors; and,

(e) a case-control study in Connecticut, subcontracted to investigators at Yale University, also focusing on occupational risk factors.

The results indicate that the most important factors in the occurrence of laryngeal carcinoma are age, smoking and alcohol consumption. Sex may not be a risk factor if environmental factors are taken into account. Age and smoking are of greatest importance while the addition of heavy alcohol consumption is more than addictive indicating a synergistic relationship between tobacco and alcohol.

Several occupations were significant in increasing the relative risk ratio after controlling for age and tobacco use. Metal processing and metal-working occupations, asbestos workers, some textile workers and certain construction workers were found to face a greater risk of laryngeal cancer from occupational exposure. For none of these workers are the findings persuasive enough yet to warrant intervention programs. However, the risk is increased to such a degreee with age, tobacco use and alcohol consumption that these individual factors in combination with the above occupational factors might indicate that older smokers working for many years in such occupations might warrant particular attention due to their elevated risk of laryngeal cancer.

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 for 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: Completed in December, 1982.

Publications:

Rothman KJ, Cann CI, Flanders D and Fried M. Epidemiology of laryngeal cancer. Epidemiologic Reviews; 2: 195-209, 1980.

Flanders WD and Rothman KJ. Interaction of alcohol and tobacco in laryngeal cancer. American J. of Epidemiology; 115: 371-379, 1982.

Flanders WD and Rothman KJ. Occupational risk for laryngeal cancer. American J. of Public Health; 72: 369-372, 1982.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1982 through September 30, 1983

UNIVERSITY OF NORTH CAROLINA, CHAPEL HILL, NORTH CAROLINA (NO1-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: $40,000

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: The total planned cohort of 60 subjects have completed the experimental study. Final data analyses are not yet complete but preliminary reports indicate the following findings regarding the type of language training most effective for preschool children with infantile autism:

1. Alternating between training in sign and in speech on the same words and phrases has been found most successful for speech and language training in language-delayed preschoolers with infantile autism.

2. Sign language training alone was found more effective than speech alone in training non vocal language delayed children with infantile autism.

3. Those language delayed children with infantile autism who are echolalic have the best prognosis for language development with training through speech.

These results have profound implications regarding the treatment of choice for delayed speech and language development in preschool children with infantile autism. Early training with both speech and sign, therefore, is indicated as

useful in most cases and the treatment of choice in many. During the research, a language training program in sign and a teaching manual for training expressive and receptive sign language in preschool children with infantile autism was developed. This sign training program was proven to be superior to training with speech alone and will be made available for use in training children with infantile autism.

Significance to Biomedical Research and the Program of the Institute: 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 examined these issues experimentally.

Proposed Course: The final phase was extended to June 30, 1983 without additional funds to allow time for report writing.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1982 through September 30, 1983

UNIVERSITY OF CALIFORNIA, SAN DIEGO (NO1-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: $175,000 (6 months only)
Annual support approximately $300,000

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 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: All of the language impaired subjects have been selected and received their first year of testing. The chronological age-matched and language age-matched normal controls are now being selected and administered their first assessment battery. A Technical Merit Review Panel reviewed the research in February 1983 and approved completion of the longitudinal study

with testing at 5, 6, 7 and 8 years of age. The language testing procedures were found to be of high scientific merit.

Subgroups of language impaired children based on their profile of expressive and receptive language functioning and phonological development have been identified. Thirty of the language impaired subjects falling into particular subtypes are being selected for a complete analysis of a transcript of 100 of their utterances annually to compare their acquisition of language functions/structures in detail with chronologically and language age-matched controls.

Significance to Biomedical Research and the Program of the Institute: 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: Following Technical Merit Review the contract will be extended for the final five years of the study to September 1988.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1982 through September 30, 1983

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 Annual Level of Support: $387,171

Objectives: To conduct a controlled clinical trial to determine the efficacy of various treatment modes for POME. The treatment consists of myringotomy (MX), myringotomy 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 2890 screening evaluations have been completed (4/83). Approximately 10% of this total have met the criteria for randomization into the four treatment groups. After randomization, the investigators have noticed a 40% attrition rate. The attrition rate has been higher than expected in that approximately 40% of the children have been disqualified prior to randomization. A total of approximately 300 patients have been randomized. Preliminary analyses of these data appear to indicate that MXTT and MXADTT offer the best treatment for POME. Questions which have not been answered are the extent to which surgical re-treatment might occur for each treatment group, surgical complications (e.g., drainage, cholesteatomas) experienced for the various groups, number of treatment failures, and number of months with consecutive or intermittment effusion.

Significance to Biomedical Research and the Program of the Institute: POME is one of the major health problems in children. Currently, there is no consensus as to the most effective treatment for this vexing problem. 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 will continue beyond the full five-year period for an additional two-year period.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1982 through September 30, 1983

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: $0

Objectives: The purpose of this contract was to determine the possible effects of hearing aid amplification on the residual hearing of children with sensorineural hearing loss. Observed hearing changes were related to the electroacoustic characteristics of the hearing aids, amount of hearing aid use, degree of hearing impairment, earmold or coupling system, etiological information and hearing deterioration unrelated to hearing aid use.

Methods Employed: Baseline audiometric and tympanometric measures have been made. Changes in threshold were measured at predetermined intervals along with dosimetry and recordings of environmental noise exposure. Complete medical genetic evaluations were obtained as necessary. Function-gain measures were 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: Subjects showing no threshold shifts are placed in the low-risk category and monitored at monthly intervals unless a significant change is noted. Subjects with a significant threshold shift (defined as a change greater than 2 standard deviations from the child's mean baseline data, but at least 5 dB) at any one of the test frequencies are placed in the high-risk category and evaluated weekly.

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 collection terminated in May 1983. Expected completion date for analyses and manucripts is October 30, 1983.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1982 through September 30, 1983

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: $0 (forward funded)

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 between fluent and stuttering children of four to 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 (DLI).

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 by the Respitrace system.

5. Lower lip and jaw movements are being measured by 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: Considerable progress has been made in simultaneous digitizing of signals of: the acoustic waveforms; electroglottographic signals of laryngeal abduction/adduction; rib cage and abdominal respiratory deflation; and electromyographic signals of obicularis oris inferior (OOI) and depressor labii inferior (DLI). This results in seven channels of data to be "processed" for movement or activity onsets and offsets. Algorithms are now being

finalized for each of the 4 sets of data, to automatically compare the timing patterns between stuttered and fluent utterances in young children evidencing stuttering between 4 and 6 years of age and between fluent and stuttered utterances of the normal and dysfluent children of the same age. Only partial data could be gathered on lip and jaw movement; many children had an adverse reaction to the strain gauges and wearing the head frame for prolonged periods.

The relationship between the length of aspiration and the stop gap in CV syllables of normal and stuttering children's speech have been compared. There is an inverse relationship between the duration of the aspiration and the stop gap in fluent speech. No such relationship was found in the stuttering children's speech indicating that the temporal coordination between onsets and offsets of labial and laryngeal gestures is unpatterned in these young stutterers.

A study of the proportion of the glottal pulse during which the vocal folds are closed indicated that stutterers had uncontrolled degrees of vocal fold abduction during phonation, in comparison with normals; this suggests that subtle abnormalities in laryngeal posturing during phonation was occurring in the stuttering children but not in the age-matched normally speaking children.

Significance to Biomedical Research and the Program of the Institute: There is a critical need to stimulate research on stuttering; NINCDS is the prime focus 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 that 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 on January 1984.

CONTRACT NARRATIVE
Communicative Disorders Program
October 1, 1982 through September 30, 1983

OHIO UNIVERSITY, ATHENS, OHIO (NO1-NS-0-2342)

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

Current Annual Level of Support: $0

FATHER FLANAGAN'S BOYS HOME, OMAHA, NEBRASKA (NO1-NS-0-2343)

Contractor's Project Director: Ronald Netsell, Ph.D.

Current Level of Support: $0

LOYOLA UNIVERSITY AT CHICAGO, CHICAGO, ILLINOIS (NO1-NS-0-2344)

Contractor's Project Director: William A. Yost, Ph.D.

Current Annual Level of Support: $0

UNIVERSITY OF CONNECTICUT, STORRS, CONNECTICUT (NO1-NS-0-2345)

Contractor's Project Director: Jay Lerman, Ph.D.

Current Annual Level of Support: $0

UNIVERSITY OF HAWAII AT MANOA, HONOLULU, HAWAII (NO1-NS-0-2346)

Contractor's Project Director: James Yates, Ph.D.

Current Annual Level of Support: $0

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. Can various types of specialists in communicative disorders learn to use terminals for interacting directly with MEDLINE and developing individualized literature searches?

3. Does MEDLINE provide 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 whose results 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, user participants 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 800 users participated in the study who were divided as to type of professional activity: faculty, clinicians, researchers, or students. These groups differed in their frequency of use of MEDLINE, the type of access they preferred for using MEDLINE services, their projected use of MEDLINE in the future and their willingness to pay for MEDLINE services. In general, researchers were those who found MEDLINE services most useful while clinicians had the lowest use of MEDLINE. Speech - language pathologists, audiologists, and otolaryngologists did not differ in their frequency of use of MEDLINE or their projected need for service.

The large majority of users felt MEDLINE services were useful for meeting their information needs along with books, journals and discussions with colleagues. Few learned to use MEDLINE independently and most preferred to submit their request to a technical information specialist (TIS) with professional training in communicative disorders. Over 80% felt that the use of a TIS in communicative sciences was necessary for satisfactory MEDLINE services and only 30% felt that the current delivery system of a non-specialized TIS librarian was adequate.

Each of the 5 contractors submitted their final report in March 1983 and will meet with NINCDS staff in June to develop recommendations based on the final results of the study.

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 will terminate in June 1983. A summary report and recommendations will be completed by staff in September 1983.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1982 through September 30, 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: $0

Objectives: The purpose of this contract was 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 is being conducted 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 relevant studies have been analyzed and ranked according to importance to the scientific knowledge of auditory effects of noise. The following manuscripts are nearing completion: Anatomical Effects of Noise; Physiological Effects of Noise; Effects of Noise on Auditory Behavior; Preservation of Hearing; Conservation of Hearing; Impulse Noise - Anatomical, Physiological and Behavioral Effects; Individual Differences; and, Biochemical 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 October 30, 1983.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1982 through September 30, 1983

TUFTS-NEW ENGLAND MEDICAL CENTER (NO1-NS-2-2305)

Title: The Prescription of Communicative Devices for Non-Speaking Patients

Contractor's Project Director: Cheryl Goodenough-Trepagnier, Ph.D.

Date Contract Initiated: June 30, 1982

Current Annual Level of Support: $240,000

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: During the first year of this research, the contractor has successfully completed development of many of the assessment procedures. Of particular importance is the development of rate prediction hardware and software systems for predicting patients' abilities to operate communicative devices. A target display panel has been assembled and uses a touch panel for patient interaction for testing patients' abilities in making movements to point, select or control switches to scan for targets for communication. Studies have been begun to determine the predictive validity of different testing sample lengths for assessment. The predictive validity of this computer assessment system will be determined in the next 2 years.

An assessment of the operational requirements of currently available communicative aids has been completed using the paired comparison technique on the following factors: spelling comprehension skills; spelling production skills; general intelligence requirements; vigilance and attention skills required; planning and production skills; sequence memory skill requirements; location memory skills; and, general memory skills required. Six different judges were used, all experienced in evaluating and prescribing communicative devices for non-vocal patients.

These judges rated nine devices on the nine skill requirement factors. There was good agreement between the judges' ratings on all factors except spelling comprehension which was highly related with reading comprehension and can be eliminated from the rating system.

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 completed in June 1985.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
October 1, 1982 through September 30, 1983

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: $89,119

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: A small microphone (1/16 inch) has been developed that can be placed in the ear canal; a procedure for coupling a driver transducer to the ear canal through an appropriate acoustic network has been developed; and, using the new microphone and driver, measurement of the frequency response of several ear canals has been accomplished. Determination of a microphone location to produce two anti-resonances in the response in the high-frequency range is nearing completion. Establishment of specifications for a satisfactory audiometer design are being initiated. Selection of a microprocessor and signal processing unit plus software development for the audiometer will be considered next.

Major Findings: Preliminary measurements on a few ear canals with the small microphone and driver transducer have shown that two anti-resonances are usually present in the frequency response at the microphone. Revised procedures for estimating the sound pressure at the eardrum from measurements at the microphone in the ear canal have been described, including a calculation that takes into account the tapered termination of the ear canal.

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: Appropriate calibration procedures for the transducers will be developed. A microprocessor-controlled audiological testing system under design will be 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.

CONTRACT NARRATIVE
Communicative Disorders Program, NINCDS
December 1, 1982 through November 30, 1983

CHILDREN'S HOSPITAL MEDICAL CENTER (N01-NS-AI-2-2666)

Title: A Double-Blind Clinical Trial to Evaluate Interferon in the Treatment of Pediatric Recurrent Respiratory Papillomatosis - A Multi-Center Proposal

Contractor's Project Director: Gerald B. Healy, M.D.

Date Contract Initiated: December 1, 1982

Current Annual Level of Support: $300,000

Objectives: Our Institute is now sharing with the National Institute of Allergy and Infectious Diseases the funding of a contract under which the efficacy of type alpha interferon in treating juvenile laryngeal papillomatosis will be evaluated.

Major Findings: Initially the intent was that the contract should be a double-blind, placebo-controlled study. However, because of the now-familiar funding problems the NIH has experienced, there were delays in implementing the study, - and in the interim it became clear that a placebo-controlled study was no longer appropriate because interferon clearly has obvious short-term benefits to offer. The present contract, now funded and underway, is a controlled study without the use of a placebo. The contract is a multicenter study under the direction of principal investigator Gerald Healy, pediatric otolaryngologist in Boston. Several other cities are included. To date June 1983 approximately 41 patients have been entered into the study.

Significance to Biomedical Research and the Program of the Institute: Juvenile laryngeal papillomata are common. The prevalence is estimated to be 1,400 to 2,000 new cases per year. It is the most common laryngeal tumor in children, which threatens the airway, and until the advent of interferon, there has been no treatment other than surgical removal. Frequent recurrence following surgery is a hallmark of the disease. Although surgical treatment is improved immeasurably with the use of the laser, the major importance of interferon has been its promise of reducing the post-surgery recurrence rate without introducing significant side effects.

Proposed Course: It is estimated that about 200 subjects will be entered into the trial, will be treated and followed for 36 months. Side effects of the interferon will be monitored carefully, as will the therapeutic effects in reducing recurrence rate.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02185-09 CDP

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Patterns of Speech Breakdown in Neurological Disease

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
C. L. Ludlow Speech Pathologist, CDP, 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:
.25	.15	.10

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
- ☐ (a1) Minors
- ☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose is to study the patterns of speech impairment associated with neuropathologies affecting different levels of the central nervous system to identify the separate functions of speech motor control and the neurological organization of these functions. Measurement of performance on different non-speech and speech tasks indicate how motor control is interfered with during involvement of particular brain structures, and the effects of neuropharmacologic treatments on speech motor control in neurologic disease.

The coordination and timing between movement onsets and offsets of the rib cage and abdominal respiratory movements, lip and jaw movements and laryngeal abduction and adduction is measured from simultaneous transduction signals during speech. In addition the velocity and displacement evaluate the limitations of each of the articulators for speech. A model of speech timing and its neurological organization is being studied to determine how speech is programmed at different levels of the central nervous system. Dysarthrias in the following forms of neurological disease are being studied: cerebellar ataxia, dystonia, Parkinson's disease, Huntington's disease and Tardive dyskinesia.

PHS 6040 (Rev. 1/83) GPO 895-100

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02247-07 CDP

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Speech and Language Abnormalities in Tourette Syndrome

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

C. L. Ludlow 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:
.10	.05	.05

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The family histories of two groups of Tourette Syndrome patients are being compared, those with disorder and those without a language processing disorder, to examine familial histories for speech and language and movement disorders in Tourette Syndrome patients. A subgroup of Tourette Syndrome patients with hyperactivity and language processing disorders in addition to vocal tics is being studied to determine the effects of haloperidol on language processing skills.

PHS 6040 (Rev. 1/83) GPO 895-100

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02336-06 CDP

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Cisplatin and Early Identification of Ototoxicity

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Earleen Elkins Audiologist, CDP, NINCDS

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 *(Use standard unreduced type. Do not exceed the space provided.)*

Cisplatin 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. Complete audiological evaluation including middle ear analysis is routinely obtained prior to administration of cisplatin and thereafter is repeated with each cycle of chemotherapy and at regular intervals afterward. Specially designed speech recognition studies are conducted at each assessment and reassessment. Data suggest a distinct dose-related hearing loss. Almost 40% of male patients followed have gone from normal hearing to requiring amplification while none of the women have shown such changes.

PHS 6040 (Rev. 1/83)

GPO 895-100

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02337-06 CDP

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Effects of Stimulants on Auditory Processing and Language Skills

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

C. L. Ludlow 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 *(Use standard unreduced type. Do not exceed the space provided.)*

A series of studies is 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.

5. The training effects of task repetition in auditory processing skills in four distinct groups of learning impaired children while not receiving drugs.

6. The effects of different neuropharmacologic agents on auditory processing and language skills in hyperactive subjects.

PHS 6040 (Rev. 1/83) GPO 895-100

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02396-05 CDP

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Auditory Deficits in Osteogenesis Imperfecta**

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Anita Pikus* Audiologist, CC

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 *(Use standard unreduced type. Do not exceed the space provided.)*

Methods are being developed to delineate the types of hearing losses associated with Osteogenesis Imperfecta (OI). Measurements 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. Current findings indicate that approximately half of the patients under 30 years of age and almost all of those over 30 years, have sensorineural hearing losses. Although some patients with OI have a stiff middle ear system similar to that seen in otosclerosis, the majority have absent reflexes and increased compliance of the middle ear, with notched tympanograms suggestive of anomalous ossicular articulation. Similar findings in otherwise uninvolved relatives suggest a genetic basis for these defects.

**This study is the NINCDS portion of a larger study (CC) entitled: "Collagen Metabolism in Osteogenesis Imperfecta (OI)."

*Dr. E. Elkins, CDP-NINCDS, is a collaborator on this project.

PHS 6040 (Rev. 1/83)

GPO 895-100

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02440-04 CDP

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Acoustic Analysis of Vocal Fold Vibration in Phonatory Pathology

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

C. L. Ludlow Speech Pathologist, CDP, 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:
.15	.10	.05

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Period length and amplitude characteristics of cycles of vocal fold vibration during phonation are being analyzed to determine how these are altered in patients with different types of vocal fold pathology. Types of vocal fold pathology being examined include: laryngeal nodules and polyps, lower motor neuron neuropathologies involving the nucleus ambiguous, upper motor neuron disease increasing vocal fold rigidity, unilateral recurrent laryngeal nerve paralysis, essential tremor affecting the larynx, spastic dysphonia, and vocal fold edema. The purpose is to determine how alterations in the morphology of the vocal folds and neurologic control affect the vibrations during phonation, in an effort to improve understanding of the physiology of normal and pathological phonation.

Hardware and software acoustic signal processing systems have been developed to allow for extraction of frequency and amplitude perturbation as well as computations of indices of tremor in phonation. Nasopharyngolaryngoscopic videotape recordings during connected speech provide interpretation of the types of phonatory pathology in various neurologic disorders. Studies are evaluating 1) which acoustic measures of phonation could be used in the identification of phonatory pathology, 2) which measures reflect perceptual ratings of voice disorders in different types of laryngeal pathology, 3) which measures are sensitive to changes in vocal fold morphology, and 4) how changes in vocal fold mass and tension alter the patterns in vocal fold vibration.

PHS 6040 (Rev. 1/83) GPO 895-100

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02441-04 CDP

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Hearing Assessment in Central Neurofibromatosis

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Anita Pikus* Audiologist, CC

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 *(Use standard unreduced type. Do not exceed the space provided.)*

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. Acoustic reflex studies and auditory brain stem response measures seem to be notably sensitive to VIII nerve neuroma. Clinical data suggest that either of these methods is likely to identify a small tumor when traditional CAT scanning measures may not. Appropriate and timely medical and audiological management plus counseling are considered for each patient individually.

*Dr. E. Elkins, CDP-NINCDS, is a collaborator on this project.

PHS 6040 (Rev. 1/83) GPO 895-100

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02464-03 CDP

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Audiologic Findings in Autism**

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Anita Pikus* Audiologist, CC

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 *(Use standard unreduced type. Do not exceed the space provided.)*

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. Some patients show previously undiagnosed mild conductive losses, amenable to medical intervention, while others show minimal high frequency sensorineural losses. Auditory brain stem response evaluations on this population are almost uniformly within normal limits.

**Part of a cooperative study with NIMH

*Dr. E. Elkins, CDP-NINCDS, is a collaborator on this project.

PHS 6040 (Rev. 1/83) GPO 895-100

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02465-03 CDP

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Hearing in Peripheral Neurofibromatosis

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Anita Pikus* Audiologist, CC

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 *(Use standard unreduced type. Do not exceed the space provided.)*

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. Approximately 60% of the patient population have diverse auditory deficits and abnormal tympanometry and acoustic reflexes. Retrocochlear abnormalities are rare. The occurrence, type and severity of auditory deficits appears unrelated to the clinical severity assigned to each NF patient. This patient population is being evaluated to provide recommendations for treatment and follow-up by the referring primary-care physicians.

*Dr. E. Elkins, CDP-NINCDS, is a collaborator on this project.

PHS 6040 (Rev. 1/83)

GPO 895-100

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02466-03 CDP

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Pediatric Oncology Regimen and Ototoxicity

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Anita Pikus* Audiologist, CC

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 *(Use standard unreduced type. Do not exceed the space provided.)*

All pediatric oncology patients on the "fever" protocol are given periodic complete audiological analyses consisting of pure tone testing, speech reception threshold, supra-threshold speech recognition, tolerance for speech tympanometry and acoustic reflex studies. Results suggest that the aminoglycoside antibiotic agents used to date with these patients, have not caused permanent handicapping hearing loss.

*Dr. E. Elkins, CDP-NINCDS, is a collaborator on this project.

PHS 6040 (Rev. 1/83) GPO 895-100

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02467-03 CDP

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Auditory Function and Cerebral Vasculitis

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Anita Pikus* Audiologist, CC

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 *(Use standard unreduced type. Do not exceed the space provided.)*

This autoimmune 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. To date, most patients demonstrate some sensorineural loss, usually without brain stem involvement. Substantial fluctuations in peripheral hearing are being observed. Auditory brain stem response (ABR) evaluations are performed as needed and seem to be a sensitive indicator of retrocochlear vascular damage. Preliminary data show some patients with abnormal ABRs following exacerbation of their illness.

*Dr. E. Elkins, CDP-NINCDS, is a collaborator on this project.

PHS 6040 (Rev. 1/83) GPO 895-100

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02468-03 CDP

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Audiologic Findings in Wegener's Granulomatosis

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Anita Pikus* Audiologist, CC

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 *(Use standard unreduced type. Do not exceed the space provided.)*

This autoimmune disease is often manifest by intractable middle ear disease 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. Fluctuating conductive hearing impairment is a prominent occurrence usually accompanied by a high-frequency sensorineural component which appears to be progressive over time. Long term audiologic follow-up is conducted in order to determine how the auditory system survives both the disease and the therapeutic regimen.

*Dr. E. Elkins, CDP-NINCDS, is a collaborator on this project.

PHS 6040 (Rev. 1/83) GPO 895-100

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02469-03 CDP

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Small Cell Carcinoma and Hearing Loss

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Anita Pikus* Audiologist, CC

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 *(Use standard unreduced type. Do not exceed the space provided.)*

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 by administering pure tones, threshold and supra-threshold speech recognition tests, tympanometry and acoustic reflex measures. Findings to date are minimal due to small enrollment of patients.

*Dr. E. Elkins, CDP-NINCDS, is a collaborator on this project.

PHS 6040 (Rev. 1/83)

GPO 895-100

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02470-03 CDP

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Audiologic Findings in an Aging Population**

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Anita Pikus* Audiologist, CC

COOPERATING UNITS *(if any)*

Clinical Center Audiology
Laboratory of Neurosciences, Gerontology Center, NIA

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 *(Use standard unreduced type. Do not exceed the space provided.)*

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. These include measures of pure tone and speech thresholds, supra-threshold speech recognition, special tests of auditory function, tympanometry, acoustic reflexes and auditory brain stem response. Aging changes are assessed by serial evaluations. Increasing loss of high-frequency hearing is the predominant finding and is consistent with other reports in the literature.

**Part of larger study with National Institute on Aging (NIA)

*Dr. E. Elkins, CDP-NINCDS, is a collaborator on this project.

PHS 6040 (Rev. 1/83) GPO 895-100

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02471-03 CDP

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Hearing and Neomycin Therapy for Type II Hyperlipidemia**

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Anita Pikus* Audiologist, CC

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 *(Use standard unreduced type. Do not exceed the space provided.)*

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 by monthly evaluation of pure tone thresholds and speech recognition measures in ipsilateral noise. At three month intervals, complete audiometric and tympanometric assessments are performed. Data indicate that no significant hearing losses have occurred in the patients under study.

**Part of larger study on Type II Hyperlipidemia and Neomycin Therapy

*Dr. E. Elkins, CDP-NINCDS, is a collaborator on this project.

PHS 6040 (Rev. 1/83)

GPO 895-100

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02557-02 CDP

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Location and Size of Brain Lesions Associated with Speech Motor Control Deficits

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

C. L. Ludlow Speech Pathologist, CDP, NINCDS

COOPERATING UNITS *(if any)*

Vietnam Head Injury Study, Walter Reed Army Medical Center

LAB/BRANCH

Communicative Disorders Program

SECTION

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.10	.10	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The goal is to better understand the brain bases for speech motor control. This research is part of a multidisciplinary investigation into the long-term functional and anatomical sequelae of penetrating craniocerebral trauma. The brain structures involved in the lesion as well as the total volume of the lesion are specified independent of the speech motor assessment. Patients exhibiting specific disorders of speech such as verbal dyspraxia, speech dysprosody, and dysarthria are selected for study. Their pattern and extent of speech impairment, other motor control deficits and neurologic impairments are related. The location and size of their brain lesions are then compared with those of other head-injured patients who are without speech or language impairment to determine whether lesions in particular brain structures are associated with chronic impairments in speech production.

Speech motor tests include the strength and range of motion and rate of movement of the lips, jaw and tongue; isolated and sequenced oral volitional movements; speech syllable repetition; word, phrase and sentence imitation; word and syllable articulation; and stress and intonation contours.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02558-02 CDP

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Audiologic Findings of Multiple Sclerosis Lymphocyte Depletion Treatment

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Anita Pikus* Audiologist, CC

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 *(Use standard unreduced type. Do not exceed the space provided.)*

There is inadequate understanding of VIII nerve dysfunction in multiple sclerosis. This study is designed to determine the role of lymphocyte depletion treatment in the fluctuations of the auditory deficit associated with multiple sclerosis. Audiological assessments are conducted prior to and following immunotherapy. They include pure tone and speech threshold measurements, supra-threshold measures of speech recognition, middle ear analyses (tympanometry and acoustic reflex studies) and auditory brain stem response evaluation. Patients have not yet completed the assessment cycle.

*Dr. E. Elkins, CDP-NINCDS, is a collaborator on this project.

PHS 6040 (Rev. 1/83) GPO 895-100

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02559-02 CDP

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Audiologic Findings in Alzheimer's Disease**

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Anita Pikus* Audiologist, CC

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 *(Use standard unreduced type. Do not exceed the space provided.)*

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 is planned to describe the nature and extent of auditory deficits associated with Alzheimer's disease in this population by documenting pure tone and speech thresholds, speech recognition tasks, middle ear status and other selected tests of auditory function.

**Part of a larger study entitled: "Regional Cerebral Glucose Utilization in Organic Dementia of the Alzheimer Type (ODAT)"

*Dr. E. Elkins, CDP-NINCDS, is a collaborator on this project.

PHS 6040 (Rev. 1/83) GPO 895-100

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02561-01 CDP

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Optimum Phonatory Functioning in Various Types of Laryngeal Pathology

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
C. L. Ludlow Speech Pathologist, CDP, 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:
.10	.10	.00

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of the research is to determine how phonatory functioning is altered in various types of laryngeal pathology, whether the concept of an optimum frequency of phonation has validity in different types of pathology and whether changing a patient's phonatory frequency alters phonatory functioning for speech. The following groups are being studied: normal males and females, patients with vocal fold nodules and polyps, and patients with unilateral recurrent laryngeal nerve paralysis.

Tasks assessing phonatory functioning include maximum phonation time, maximum speaking time and counting for one minute. These tasks are performed under five experimental conditions during which phonatory frequency and intensity are manipulated systematically.

Measures evaluating phonatory function assess the duration of phonation and speaking time on one exhalation, acoustic power per respiratory volume and the stability of vocal fold vibration.

These studies will determine the validity of the concept of "optimum pitch" currently used in treatment of many voice disorders. Improved understanding of how the functioning of the larynx is compromised in different types of pathology and whether functioning is improved at different phonatory frequencies is important for furthering understanding of the phonatory mechanism in different types of pathology and new directions for treatment.

PHS 6040 (Rev. 1/83) GPO 895-100

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02562-01 CDP

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Characteristics of Voice Disorders of Unknown Etiology

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

C. L. Ludlow Speech Pathologist, CDP, 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:
.10	.10	.00

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose is to compare the patterns of vocal fold vibration and the impairments in phonatory functioning found in patients with voice disorders of unknown etiology with those of patients with known neuropathologies affecting phonation to determine whether particular neuropathologies are implicated in phonatory disorders of unkown etiology. Vocal fold vibration and phonatory functioning is being analyzed in patients with spastic dysphonia and vocal tremor and compared with those of patients with known neuropathologies of the recurrent laryngeal nerve, and lower motor neuron and upper motor neuron disorders affecting laryngeal functioning. Laryngeal reflexes and respiratory functioning are being evaluated in these groups to determine the integrity of phonatory functioning. The effects of manipulating phonatory functioning through alterations in auditory feedback is being evaluated for identifying particular subtypes of these disorders which are predictive of the effects of different treatment approaches.

PH S 6040 (Rev. 1/83) GPO 895-100

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02563-01 CDP

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Effects of Rate Manipulation on Speech Motor Control in Dysarthria

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

C. L. Ludlow Speech Pathologist, CDP, 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:
.10	.10	.00

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of the research is to determine the ability to alter movement displacement, velocity, and timing, through the manipulation of speaking rates in patients with neuropathologies at different levels of the central nervous system. Speech rate is manipulated both extrinsically (using timers, and delayed auditory feedback) and intrinsically by patients during imitation of speech tokens. The effects of increasing and decreasing speech rate on speech articulator movement displacement and velocity is being studied to determine whether an optimum speech rate can be found in individual patients and whether this differs according to which CNS structures are involved. Further, the effects of speech rate manipulation on the coordination and pattern of timing between movement onsets and offsets is being examined to determine whether time patterning remains intact in different types of neurologic disease. The purpose is to identify those neurologic structures involved in maintaining time phase relationships between the articulators in speech motor control.

The onset and offset of movements of the rib cage, abdomen, lips, jaw and larynx are being studied for change in different rate conditions in the following types of neurologic disease; cerebellar ataxia, dystonia, Parkinson's disease, and Huntington's disease.

PHS 6040 (Rev. 1/83) GPO 895-1 00

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02564-01 CDP

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Relationship of Language and Speech Deficits to Subcortical Neuropathologies

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

C. L. Ludlow Speech Pathologist, CDP, NINCDS

COOPERATING UNITS *(if any)*

Intramural Research Program, NINCDS
Vietnam Head Injury Project, Walter Reed Army Medical Center

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 *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose is to determine whether language processing and expression deficits are associated with neuropathologies affecting subcortical structures and whether such language deficits contribute to such patients' speech motor control deficits. Neurolinguistic studies of language functioning are aimed at analyzing the patterns of language deficits in patients with the following neuropathologies: Parkinson's disease, Huntington's disease, and penetrating head injuries involving subcortical structures. The following issues are being addressed: whether the language processing deficits are related to disease duration, memory impairment, ability to retrieve previously learned material, motor deficits, speech motor control deficits and, in the case of penetrating head injuries, the size and location of the subcortical lesion. At issue are whether different patterns of language impairment appear in different types of neuropathology and whether these vary independent of disorders of speech motor control.

The language functions being addressed include: syntactic comprehension and formulation, naming, speech repetition, word fluency, and reading and writing skills.

PHS 6040 (Rev. 1/83) GPO 895-100

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02565-01 CDP

PERIOD COVERED

April 1, 1983 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Audiologic Findings in Vogt-Koyanagi-Harada (VKH) Syndrome

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Anita Pikus* Audiologist, CC

COOPERATING UNITS *(if any)*

Clinical Center Audiology

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 *(Use standard unreduced type. Do not exceed the space provided.)*

This disorder is better known for the opthalmologic findings of retinal detachment and a variety of neurological manifestations such as cranial nerve palsies, mental changes and hemiparesis. Little is known of audiological findings other than patient reports of hearing loss and tinnitus. The test protocol is sufficiently broad to include middle ear function and cochlear evaluation as well as auditory brain stem responses.

*Dr. E. Elkins, CDP-NINCDS, is a collaborator on this project.
This is a cooperative study with Dr. Nussenblatt (79-EI-49 and 81-EI-33) of the National Eye Institute, Clinical Branch.

PHS 6040 (Rev. 1/83)

GPO 895-100

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02566-01 CDP

PERIOD COVERED

March 1, 1983 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Audiologic Findings in Twins with Alzheimer's Disease

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Anita Pikus* Audiologist, CC

COOPERATING UNITS *(if any)*

Clinical Center Audiology
Laboratory of Neurosciences, NIA
Laboratory of Cerebral Metabolism, NIMH

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 *(Use standard unreduced type. Do not exceed the space provided.)*

Changes in cognition as well as other neurologic involvements occur during aging and in organic dementia of the Alzheimer type. Accompanying changes in the auditory system have not been previously defined. This unique population offers the opportunity to evaluate one twin with the disease and to evaluate the other as his/her control. Pure tone and speech threshold, tests of speech recognition, tests of middle ear function and auditory brain stem function are being obtained. No data are reportable at this time.

*Dr. E. Elkins, CDP-NINCDS, is a collaborator on this project.

PHS 6040 (Rev. 1/83) GPO 895-100

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02395-05 CDP

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Analysis of Fluctuating Hearing Loss Associated with Cogan's Syndrome

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Anita Pikus* Audiologist, CC

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:
.01	.01	.00

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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.

This study has been completed.

*Dr. E. Elkins, CDP-NINCDS, is a collaborator on this project.

PHS 6040 (Rev. 1/83) GPO 895-100

TAB 4 -- FUNDAMENTAL NEUROSCIENCES PROGRAM -- FNP

ANNUAL REPORT
October 1, 1982 through September 30, 1983
Fundamental Neurosciences Program
National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

CONTRACT NARRATIVES (CONTINUED)

ANNUAL REPORT
October 1, 1982 through September 30, 1983
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 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 stimulaton, corrosion of 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 2.8 million dollars a year.

GENERAL FUNDAMENTAL NEUROSCIENCES

On June 8, 1983, there were 484 regular research grants, 13 new investigator research awards and 12 program project grants in the program (see tables). Neurophysiology and neurochemistry together accounted for about 75% 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, two were in neurochemistry, two were in neuroanatomy and one each in neuropsychology and biomedical engineering. The number of new investigator research awards more than doubled. 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 1983

	Number	% of Total	$	% of Total $
Neuroanatomy	63	13.0	5.1M	12.6
Neurophysiology	194	40.1	15.5M	38.3
Neurochemistry	171	35.3	14.7M	36.3
Neurobiology	18	3.7	1.8M	4.4
Neuropsychology	20	4.2	1.7M	4.2
Neural Prostheses and Biomedical Engineering	14	2.9	1.2M	3.0
Scientific Information	4	.8	.5M	1.2
TOTALS	484	100.0	40.5M	100.0

FUNDAMENTAL NEUROSCIENCES PROGRAM

ACTIVE NEW INVESTIGATOR RESEARCH AWARDS
JUNE 1983

	Number	$
Neuroanatomy	3	142K
Neurophysiology	3	148K
Neurochemistry	5	247K
Neural Prostheses	2	98K
TOTALS	13	635K

FUNDAMENTAL NEUROSCIENCES PROGRAM

ACTIVE PROGRAM PROJECT GRANTS
JUNE 1983

	Number	% of Total	$	% of Total $
Neuroanatomy	2	17	1.0M	26
Neurophysiology	6	50	1.6M	41
Neurochemistry	2	17	.8M	20
Neuropsychology	1	8	.3M	8
Biomedical Engineering	1	8	.2M	5
TOTALS	12	100	3.9M	100

Neurophysiology of Cognitive Processes

This program announcement, originally issued in July 1980, emphasizes the program's continuing interest in promoting research on the biological basis of higher brain function. Fifty-five applications were received and 18 awards were made. A number of the studies involve event-related potentials in animals and man. Two program projects were funded, one in cognitive neurosciences and one in behavioral neurology. In November 1982, the announcement was reissued and ten applications have been received for the October 1983 NANCDS Council meeting.

Bilateral Asymmetry of the Brain

One of the fruitful areas of research relating complex behavior to characteristics of the brain deals with the functional and anatomical asymmetry of the brain. A group of scientists supported by the FNP is in the forefront of efforts to describe the histological aspects of the asymmetry in human and animal brains. Another team is studying the effects of separating parts of the hemispheres by neurosurgery of the corpus callosum (in treating epilepsy). A third group is relating direct measurements of brains, obtained from cancer volunteers, with psychological test scores obtained before death.

Neuroimmunomodulation

The nervous system and the immune system are interrelated anatomically, physiologically, and ontogenically. The term, neuroimmunomodulation (NIM), is shorthand for the multiple influences of the nervous system upon the immune responses of the entire body. NIM also includes the influences of the immune system upon the nervous system as well as the multiple feedback loops interconnecting the two; interactions can occur via circulatory routes (hormones and other chemical messengers) or via direct neural fiber connection.

Current research in the field includes studies on (a) effects of brain lesions upon antibody production, cellular immunocompetence, anaphylaxis, and thymus and bone marrow functions; (b) changes in immune responses associated with classical or instrumental conditioning, or other psychological changes; (c) changes in unit activity of neurons in the central nervous system during the course of immunogenesis; (d) influences of environmental changes, mediated by neural or neurohormonal mechanisms, leading to alteration of immune competence; (e) studies of receptor sites on cellular elements (i.e., lymphocytes) of the immune system for transmitters, and neurally-active polypeptides, and (f) anatomical investigation of the common embryological origins and parallel development of various tissues of the immune and nervous systems.

The Fundamental Neurosciences Program wishes to encourage research in this potentially highly significant but not widely appreciated area which should lead to a better understanding of the mechanisms of interactions among the nervous, endocrine, and immune systems. This in turn should eventually have enormous potential for applications to clinical and preventive medicine.

This year together with the National Institute of Allergy and Infectious Diseases, we will issue a program announcement indicating our intention to encourage further applications in the field of NIM.

NEURAL PROSTHESIS PROGRAM

Significant advances were made in understanding basic problems in both neuroscience and technology which are preventing the development of clinical useful neural prostheses. For example, a method of bonding the insulator, Parylene C, to metallic electrodes and implantable electronic stimulators that was developed under contract, has successfully passed in vitro testing. This is the only known method of non-mechanical bonding of Parylene to substances other than itself. Both histopathological and electrochemical studies of toxic effects of stimulating electrodes and stimulating currents have indicated that as electrode surface area is reduced, higher charge densities can be passed before tissue damage occurs. Iridium continues to be the most promising new metallic electrode material and preliminary histopathological test results are encouraging. The clinical testing under contract of the neurogenic bladder evacuation prosthesis has been plagued with start-up problems, some of which were caused by NIH. Most of these now appear to be solved and the first patient should receive a bladder prosthesis before the end of this fiscal year. For details of all Neural Prosthesis Program projects, see the contract narrative section.

BIOMEDICAL ENGINEERING 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 (BEP). A new grant for the development of implantable neuromuscular stimulators for use in rehabilitation of quadriplegic patients was initiated. This grantee will work closely with a Neural Prosthesis Program contractor who has developed implantable stimulators for use in auditory prostheses. Significant progress has also been made in a project that is developing multichannel single unit recording arrays for recording electrical activity from individual neurons in cortical cell columns. Prototype passive probes (no active electronics in the recording probe) have been fabricated using photolithographic thin techniques and have been used to successfully record single unit activity in acute preparations. Much work remains, however, before multichannel chronic probes are available with signal processing electronics self-contained in the probe structure.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1982 through September 30, 1983

Contractor: EIC LABORATORIES (NO1-NS-2-2303)

Title: Development of Neural Stimulating Electrodes and Evaluation of their Electrochemical Reactions

Contractor's Project Director: Barry Brummer, Ph.D.

Date Contract Initiated: August 28, 1982

Current Annual Level of Support: $156,245

Objectives and Methods Employed: The electrochemical processes that occur at the electrode-electrolyte interface of stimulating electrodes and methods of reducing undesirable reactions are being studied. The simulated extracellular fluid in which electrodes have been pulsed is analyzed with the goal of developing electrodes and stimulus regimens that reduce undesirable electrochemical reactions.

Major Findings: Iridium oxide films have been prepared by the thermal decomposition of $IrCl_3$ deposited from a solution onto titanium wire substrates. Cyclic voltammetry and biphasic pulse experiments have demonstrated a 50-fold increase in charge capacity of iridium oxide coated titanium electrodes compared to uncoated titanium electrodes. It is apparent that a period of hydration is required in order to utilize full charge capacity of thermally prepared iridium oxide films. Preliminary evidence indicates that iridium oxide films are mechanically and chemically stable in protein-containing saline electrolytes. Experiments have shown that 5M sulfuric acid is a satisfactory solution in which to shape conical tips on iridium microelectrodes.

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 is the first year of a three-year contract.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1982 through September 30, 1983

Contractor: ELECTROCHEMICAL TECHNOLOGY CORPORATION (N01-NS-0-2316)

Title: Electrochemical Studies

Contractor's Project Director: Dr. Theodore Beck

Date Contract Initiated: December 1, 1979

Current Annual Level of Support: $138,886

Objectives and Methods Employed: New stimulation electrodes based on ion selective membranes are being developed and fabricated.

Major Findings: Aging tests of ion exchange membranes in sodium chloride solution indicate that the anion transference number does decrease slowly with time and the rate increases with temperature, but the rate appears to be acceptable at 37 degrees centigrade. High current density pulsing of electrodes to determine the upper limit of operation has indicated that at current densities of 4-10 amperes/cm^2, growth of porous silver occurs on the silver/silver chloride electrodes. The porous silver growth stopped at about 40 microns of thickness suggesting that a preformed porous layer may be used for high current density electrodes.

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 was renewed for an additional three years. This is the first year of the three-year renewal.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1982 through September 30, 1983

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: Arrays of microelectrodes with surface areas of $2 \times 10^{-5} cm^2$ were implanted in precruciate gyrus of cats. The animals were stimulated with current pulses of 30 microamperes and a charge density of 300 microcoulombs/cm^2 per phase. Negligible neural damage during 24 hours of continuous stimulation was seen and this was the highest charge density at which this result was found. Stimulus current of 10 microamperes was required to evoke a direct (short latency) component of evoked response in the pyramidal track signal so the stimulus signal employed during 24 hours of stimulation was at least three times that required to activate neurons near the electrode. Studies of the access resistance and capacitance of electrodes during long-term stimulation have indicated that the metal tissue interface remains relatively stable after the first 48 hours of stimulation, but that significant fluctuations can occur during the first 48 hours. In studies of histopathological reactions around electrodes, no significant difference was observed in cortex adjacent to either platinum 30% iridium or electrodes made of pure iridium. Both were surrounded by a few mononuclear cells along the electrode shafts and near their beveled tips. The rest of the tissue appeared normal including neurons immediately adjacent to the tip. Studies of chronic stimulation through these same types of electrodes are under way.

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 contractor was successful in winning a competitive renewal and a renewal is presently being negotiated.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1982 through September 30, 1983

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: A method of linearizing forced transducers was developed based on lookup tables in read-only memory of a computer. A new controller has been designed for closed loop digital control of paralyzed muscle. This design allows for greater variability in changes of muscle characteristics and is based on the root locus method. The design of force sensor transducers has included the use of two pressure transducers in the same force sensor, prestressing the gel within the transducer, and using a hermetically sealed oil filled transducer. Monitoring equipment has been constructed for detecting the position and force of the thumb in individuals who are paralyzed from injuries to the C5-C6 region and who are undergoing functional neuromuscular stimulation of their paralyzed upper extremity.

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 contract will be completed during this fiscal year and a competitive renewal is anticipated.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1982 through September 30, 1983

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: Restricted lesions of motor cortical areas, even those described in literature which should produce some degree of motor impairment, have not been effective in producing significant modifications in voluntary movement, nor do these restricted lesions faithfully reproduce clinical syndromes of spasticity. Investigations were initiated to determine whether ACTH injections in the brainstem of cats would produce changes similar to those observed in spasticity. Also, attempts to produce movement disorders in cats using injections of Kainic acid have been made. Four of eight animals developed arrhythmic movement of the fore and hind limbs mimicking local motor movements. However, the animals exhibited little postural control. In three animals, a wide-based gait and steady locomotion were present during the first week. However, no permanent reflex or voluntary movement deficit persisted in these animals. Cerebellar stimulation resulted in a cessation of the large amplitude rhythmic movements and oscillatory patterns in the EMG. Injecting ACTH in the vicinity of the locus ceruleus has produced transient rigidity in all four extremities. The animals had considerable difficulty ambulating and exhibited stiff movements in all extremities.

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 contract will terminate in September 1983.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1982 through September 30, 1983

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 a 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: A four element force sensor array was delivered to the University of Utah Center for Biomedical Design for mounting on an artificial arm. The transmitter and receiver electronics with a four element multiplexer section was also delivered as part of the system. The transducer will be attached to a prosthetic hook and will be connected to a tactile feedback system. Laboratory tests of force sensor arrays indicate that they have the nonlinear behavior which stress-strain characteristics predict for rubber compression. An electronic circuit has been developed which linearizes the voltage output of the transducers. This will allow simple summing of voltages from each array element in the transducer to produce a signal proportional to the total force.

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 contract will expire in February 1984. This contractor was unsuccessful in winning a competitive renewal. The winning contractor was Case Western Reserve University and the new principal investigator will be Dr. Michael Newman.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1982 through September 30, 1983

Contractor: STANFORD UNIVERSITY (NO1-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 multielectrode arrays for stimulation of the eighth nerve. These electrodes will be used for the evaluation of the feasibility of multichannel auditory prostheses.

Major Findings: The construction of thin-film electrodes was temporarily halted due to the inability to achieve adhesion between flexible substrates and conducting metalization. Silastic electrodes of the Hochmair type were fabricated and one eight-electrode model was implanted in a deaf subject.

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 contract is in the final year of a three-year contract.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1982 through September 30, 1983

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: The histopathological sequelae of otitis media in cochleas that have been implanted with cochlear electrodes have been studied. Extensive new bone growth occurs in the scala tympani which can displace the electrode from its original position. The results indicate that otitis media could greatly alter the sensorineural structures available for electrical stimulation at practical threshold levels.

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 final year of a three-year contract.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1982 through September 30, 1983

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: Pinhole problems in the gate oxides of custom fabricated transistors were traced to the attack of the oxide by hydrogen fluoride (HF) etch. The solution to the problem was to rearrange the geometry so that the contact holes were never positioned above a gait oxide and to minimize the time in the HF etch. Discontinuities in metal conductors were eliminated by incorporating a phosphorus glass reflow step which smooths out the surface. Variations in dopant drive-in times have been studied. A satisfactory compromise time was selected which is not so long that dopants penetrate the protective oxide, nor so short that the dopant silicon region is too thin resulting in subsequent metal contacts which "spike through" during subsequent process steps. The primary layout of a new current source chip and its mask were completed. A new regulator based on a 36 volt breakdown kit chip has been completed. Also, a new low power fm detector based on the 36 volt kit chip has been developed. The transmitter has been redesigned eliminating eight parts from the previous design. Also with the new design, the transmitter can be put into a package the size of a quarter so that integration with the transmitter coil seems feasible. This reduces the problem that capacitance caused in the long cable between the transmitter coil and the previous transmitter design.

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 contract is in the second year of a three-year contract.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1982 through September 30, 1983

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: The preliminary measurements of capacitance and dissipation factor of $BaTiO_3$ films annealed in air at temperatures of 900 to 1300 degrees centigrade indicate dielectric constants of 300 to 5,400 and capacitance in the range of 10 to 38 nF/mm^2 at 2kHz as measured with the ac bridge. The dissipation factors ranged from 11% to 64%. The dc leakage currents of the films at 1 volt vs a standard calomel electrode were 1 to 20 nA/mm^2 indicating that the films had poor leakage resistance. Films of barium titanate were sputtered and heat treated. A 10,000 angstrom thickness appears to be the minimum necessary film to achieve coherent films. The high leakage current is primarily at sites of bare platinum where poor coverage occurred.

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 second year of a three-year contract.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1982 through September 30, 1983

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: The mechanical properties of Parylene C deposited at different thicknesses were studied. Apparently, a thickness of about 6 microns represents a threshold value above which elongation rises dramatically. Tearing of samples was observed in the region of 2-6 microns. Parylene C deposited at -60 degrees centigrade has a "villous morphology." The possibility of using such a structure to increase structural stability by fibrous ingrowth was suggested. Evaluation of iridium electrodes polished on a lead disc was carried out using the SEM/KEVEX electron spectroscopy unit. No lead or lead-containing compounds (within the resolution of the unit) were present in the electrode samples. The effect of dry aging on self-supported Parylene C films was studied. A significant increase in dielectric constant was seen with time. A repeated flex testor for small diameter wires has been designed and construction initiated. Parylene C films that are annealed at 200 degrees centigrade for two hours show a large increase in crystallinity.

Significance to Biomedical Research and to the Programs 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 second year of a three-year contract.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1982 through September 30, 1983

CONTRACTOR: UNIVERSITY OF MICHIGAN (NO1-NS-1-2384)

Title: Multichannel, Multiplexed, Intracortical Recording Electrode Arrays

Contractor's Project Director: Dr. Ken Wise

Current Annual Level of Support: $189,000

Objectives and Methods Employed: Develop miniature, multichannel, multielectrodes 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: Two substrate shapes for passive electrode probes have been designed and fabricated. The probes contain three recording electrodes. One site is at the tip of the carrier while the remaining two are at a distance of 1 mm behind the tip. The carrier thickness is about 20 microns. Successful single-unit recording from the tip electrode has been achieved. A custom integrated circuit implementing the implantable probe electronics has been successfully fabricated and a setup for testing this circuitry has been assembled and is functional. Preliminary tests have established the feasibility of amplifying, multiplexing, demultiplexing, and reconstructing neural signals having amplitudes less than 20 microvolts with good fidelity. All probe electronics are functional except for the two-phase clock splitter which will require a redesign in the next chip iteration.

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 second year of a three-year contract.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1982 through September 30, 1983

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: $131,091

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: Using gold-coated alumina substrates, a determination was made of the moisture resulting from ionic diffusion through several different types of insulating materials. The test fixtures with the insulating coatings were immersed in 0.9% salt solution and the conductive patterns on the substrates were monitored for leakage currents. The conducting patterns were stressed with 9 volts dc. The following coatings failed to prevent significant leakage occurring between the conductive metalization patterns: Pyralin PI-2540, Pyralin PI-2555, HR 605P and Parylene C. These failures occurred over tests period as short as three hours and as great as 3,984 hours. Also, immersion tests of inorganic coatings including silicon nitride laid down by the photo-CVD process and photox silicon dioxide in thicknesses of 3,500 to 5,800 angstroms failed after only one hour in the salt water solution. The latter failures were attributed to pinholes or insufficient coverage.

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 second year of a three-year contract.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1982 through September 30, 1983

Contractor: GINER, INC. (NO1-NS-2-2392)

Title: Development of Improved Capacitor Stimulating Electrodes

Contractor's Project Director: David Wong, 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: Attempts have been made to anodize titanium in a barium-EDTA solution. Preliminary experiments with titanium wires anodized to 5 volts did not yield higher capacitance values or lower leakage currents than control wires anodized in sulfuric acid. The potentiostatic anodization of titanium foil electrodes was studied. The use of low current density and slow oxygen evolution allows the oxide layer to cover the exposed titanium pits resulting in leakage currents dropping to very low values.

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 second year of a three-year contract.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1982 through September 30, 1983

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: $90,939

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: A regional urodynamic laboratory has been installed at McMaster and will be working closely with this project. The informed consent document has had to be revised in light of some criticisms from legal advisors and on the recommendation of NIH. The final document has now been approved by both McMaster and NIH. No humans have been implanted yet because of a reorganization in the electronic company which was to supply the electrodes, implanted stimulators, and transmitters. This supplier has failed to meet several deadlines and a new supplier has been contacted.

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 second year of a three-year contract.

CONTRACT NARRATIVE
Fundamental Neurosciences Program, NINCDS
October 1, 1982 through September 30, 1983

Contractor: RFP-83-06

Title: Speech Processors for Auditory Prostheses

Contractor's Project Director: To be determined

Date Contract Initiated: To be determined

Current Annual Level of Support: To be negotiated

Objectives and Methods Employed: Substantial progress has been made in the development of implantable electrodes and receiver-stimulators for multichannel, auditory prostheses. Prototypes of these devices have been evaluated in human subjects and preliminary psychophysical data have been obtained. It is evident from this data that considerable processing of the raw speech signal will be required to match it to the narrow bandwidth, limited dynamic range multichannel implants. It is anticipated that this project will permit the design and fabrication of both a relatively flexible laboratory-based speech processor during the first phase and construction of miniaturized wearable version designed for specific patients during the second phase.

Major Findings: There are no major findings as this contract is not yet under way.

Significance to Biomedical Research and to the Program of the Institute: Auditory prostheses for individuals with sensory deafness may provide a means of communucation for this class of deaf individuals. The NINCDS is committed to determining the feasibility of auditory prostheses for the deaf.

Proposed Course of Contract: The first year of a two-year contract will begin before September 30, 1983.

TAB 5 -- CONVULSIVE, DEVELOPMENTAL & NEUROMUSCULAR DISORDERS -PROGRAM -- CDNDP

ANNUAL REPORT
October 1, 1982 through September 30, 1983

Convulsive, Developmental and Neuromuscular Disorders Program
National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

ANNUAL REPORT
October 1, 1982 - September 30, 1983

CONVULSIVE, DEVELOPMENTAL AND NEUROMUSCULAR DISORDERS PROGRAM
NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS AND STROKE
NATIONAL INSTITUTES OF HEALTH

ORGANIZATION OF REPORT

The Annual Report has three main sections. The first section is a brief administrative summary of the Program, followed by reports from the Developmental Neurology and Epilepsy Branches respectively.

PROGRAM SUMMARY STATEMENT

The Convulsive, Developmental, and Neuromuscular Disorders Program (CDNDP) 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 any of the medical neurological disorders within the following categories: Convulsive and Related Paroxsymal Disorders, Muscular and Neuromuscular Disorders, and Neurological Disorders of Early Life.

Organizational Changes in FY 1983

The Convulsive, Developmental, and Neuromuscular Disorders Program was formed at the end of FY 83 from what was formerly called the Neurological Disorders Program. Convulsive and related paroxsymal disorders, including sleep research, continue to be administered within the Epilepsy Branch. Muscular and neuromuscular disorders as well as neurological disorders of early life are administered within the Developmental Neurology Branch.

Grant Activity

The major mechanism of Program support is the investigator-initiated research grant application. During FY 83, the Program published four program announcements designed to encourage research in areas where it has been determined that additional effort is appropriate. Two of the announcements were to strengthen Program emphasis on neurological disorders of early life, including the Neurobiology of Autism, and research relating to Neurofibromatosis and Related Phakomatoses.

The Epilepsy Branch in FY 83 published two program announcements - one seeking grants to develop a small animal model for screening antiepileptic drugs, and the other announcement requesting research grants in the area of hormones and epilepsy.

Highlights of research findings from grants supported by the Program are presented in the subsections of the reports of 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 being tested in all phases of drug development from drug synthesis to clinical trials. 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 two monographs and several related articles in FY 83. Additional monographs are in various stages of preparation. The Users Guide to the NCPP Data has been created 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 1983

1) Program Advisory Committee. The Convulsive, Developmental and Neuromuscular Disorders Program Scientific Program Advisory Committee (SPAC) met early in the fiscal year to provide guidance for Program activities. The Committee members are:

Peggy C. Ferry, M.D.	University of Arizona
John M. Freeman, M.D.	Johns Hopkins University
Robert G. Grossman, M.D.	Baylor University
J. Murdoch Ritchie, Ph.D., F.R.S.	Yale University
Hugo Gonzalez-Serratos, M.D., Ph.D.	University of Maryland
Vivian Shih, M.D.	Massachusetts General Hospital
Joseph J. Volpe, M.D.	Washington University
Arthur A. Ward, M.D.	University of Washington

2) CDNDP Sponsored Workshops and Conferences. CDNDP has taken three steps to implement staff interest in the development of useful models for neurological diseases. These steps included a one-day meeting of veterinarians in Bethesda focusing on establishment of a liaison between practitioners and NINCDS. In addition, CDNDP met with the American College of Veterinary Pathology and the American College of Veterinary Internal Medicine at their annual meetings to express our interest in recognizing useful animal models. Finally, CDNDP initiated a program announcement to develop animal models of neurological disease and/or to analyze and compare existing models.

In late FY 83, CDNDP hosted a workshop on definitional issues for autism research. The purpose of this workshop was to develop a document addressing definitions of autism and related syndromes. This workshop provided an explicit operational basis for the application of technologically advanced neurobiological methods to the study of autism.

CDNDP hosted the first of a series of follow-up meetings with the Health Voluntary Agencies. Several groups representing developmental neurological disorders presented an update of activities since the first round of meetings three years ago.

TAB 5.A -- EPILEPSY BRANCH -- EB/CDNDP

ANNUAL REPORT

October 1, 1982 through September 30, 1983

Epilepsy Branch, CDNDP

National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

ANNUAL REPORT
October 1, 1982--September 30, 1983

Epilepsy Branch
Convulsive, Developmental and Neuromuscular Disorders Program
National Institute of Neurological and Communicative Disorders and Stroke
National Institutes of Health

The Epilepsy Branch commitment 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 1982. They are supported by the contract and direct operations mechanism as will a major new clinical trial on the prevention of Posttraumatic Epilepsy which will begin in the fall of 1983.

Several personnel changes occurred among the Epilepsy Branch professional staff during the year. Yu Liyun, M.D., from Shanghai, China, joined the staff as a WHO Neurosciences Fellow. Izet Kapetanovic, Ph.D., joined the staff as a pharmacologist while Kathleen Swisher, R.N., assumed the position of Clinical Trials Monitor.

The NINCDS Antiepilepitc Drug Development (ADD) Program has remained effective in interesting pharmaceutical companies to pursue the development of new drugs for the treatment of seizures. The screening project received over 1,000 chemicals to determine possible anticonvulsant activity. These chemicals were evaluated by its contractor, the University of Utah. Ninety-one day rat and dog toxicity studies continued at Southern Research Institute under contract through June with a new contract awarded in July. 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 ADD 03055 in addition to two task orders each for the clinical evaluation of two new drugs, ADD 35002 and ADD 40016, in partial seizures. This year, task orders were awarded for the clinical evaluation of a new antiepileptic drug as well as the pharmacokinetic evaluation of another new antiepileptic drug. 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 Preclinical Pharmacology Section of the Epilepsy Branch continues to provide information and support for the preclinical aspects of the ADD Program. Section personnel review data from the screening and toxicology contracts. This function maintains the continuity and flow of new compounds for NINCDS sponsored efficacy trials. Laboratory personnel have developed methods of analysis for two new drugs which are presently undergoing clinical efficacy trials. These methods have been taught to the laboratory technicans of the multicenter collaborative efficacy trials.

An in vitro model of evaluating the potential of drug-drug interactions between new drugs and phenytoin and/or carbamazepine has been developed. Early identification of such interactions are needed prior to clinical studies in order to prevent unwanted toxicity. This model, which uses microsomes derived from rat liver, has been found to be predictive of interactions in humans. The interaction of a new anticonvulsant, nafimadone, and phenytoin is now under investigation.

A new in vitro model which appears to be useful in screening for potential antiepileptic drugs has been developed. This model uses mouse brain slices from the hippocampus. Seizures are induced with the addition of pentylenetetrazole. The frequency and amplitude of the electrical discharge of the CA_3 cells are recorded. New chemical entities are now being evaluated for their ability to block these induced seizures.

Through many different means, the Epilepsy Branch in FY 83 has remained actively involved in all aspects of epilepsy activities. Contracts have been awarded or are already ongoing to evaluate antiepileptic drugs in a series 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 aided in the planning and organization of the Epilepsy International Symposium which was held in Washington, D.C., in September 1983. Many national and international visitors participated in the 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.

GRANT SUPPORTED RESEARCH

Significant advances in understanding the role of GABA and the benzodiazepine receptor complex in neuronal activity were made in FY 83. It is anticipated that these developments will provide more insights for the treatment of more than two million Americans suffering from epilepsy.

In FY 83, CDNDP received 119 applications for research and support of convulsive and related paroxysomal disorders, of which 99 were approved and 35 funded for a total of $2,883,355. Of the funded applications, 20 were new or supplemental awards for $1,086,781. There are currently 81 active grants totaling $11,158,421.

The majority 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.

A fundamental question to be answered in epilepsy research 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 normal cells can produce a "burst" or an 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. The electrotonic coupling exists in both the neocortex and the CA_1 region of the hippocampus. Although research indicates that the number of such connections are relatively small, electrotonic coupling does contribute to the synchronization process. Further research has shown that there is a percentage 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 CA_3 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 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 results 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 GAD binding.

Neuropeptides probably play a significant role in the generation or control of abnormal discharges. For example, somatostatin increases the excitability of CA_1 cells in the hippocampus similar to the effect of glutamate. More often, it has been shown that there is a change in the presynaptic terminals which may be an indirect effect of the hormone. The peptides arginine-vasopressin and oxytoxin increase cortical excitability and can induce seizures. Arginine-vasopressin in the hippocampus can evoke increases in excitation of CA_1 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 postsynaptic 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. A major effort is underway to find an endogenous ligand for the benzodiazepine receptor. GABA related excitants such as bicuculline, penicillin, 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 pentylenetetrazole prevent barbiturate binding and decrease inhibition. Seizures themselves have been shown to increase the number of benzodiazepine receptors.

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 will enhance the activity of GAD, the enzyme responsible for production of GABA.

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.

CONTRACT NARRATIVE
Convulsive, Developmental, and Neuromuscular Disorders Program
Epilepsy Branch
October 1, 1982--September 30, 1983

UNIVERSITY OF KANSAS MEDICAL CENTER (NO1-NS-2-2313)

Title: Investigation of Pharmacologic Posttraumatic Epilepsy Prophylaxis

Contractor's Project Director: Charles Brackett, M.D.

Date Contract Initiated: June 28, 1972

Current Annual Level: 0

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 selected for 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 analyses 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 contract expired May 15, 1983.

Publications: White, B.G., Pharmacological prophylaxis of posttraumatic epilepsy reconsidered. Epilepsia (In press).

White, B.G., Penry, J.K., Brackett, C.E., et al, Pharmacological prophylaxis of posttraumatic epilepsy. Prophylactic and therapeutic doses. Epilepsia (In press).

CONTRACT NARRATIVE
Convulsive, Developmental, and Neuromuscular Disorders Program
Epilepsy Branch
October 1, 1982--September 30, 1983

SOUTHERN RESEARCH INSTITUTE (NO1-NS-0-2327), Birmingham, Alabama

Title: Studies of Toxicology and Selected Pharmacology of Potential Anticonvulsants

Contractor's Project Director: Robert Meeks, Ph.D.

Date Contract Initiated: March 1, 1979

Current Annual Level: $550,000

Objectives:
1. Oral toxicity of candidate anticonvulsant compounds in beagle dogs and rat: This portion of the toxicity evaluation exposes potential toxicologic effects 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 the 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 Commmittee has established priorities for the toxicologic evaluation of the compounds. Supplies of several compounds (2-5 kg) were requested from the supplier. For each compound, a protocol is 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 03046, ADD 09004). In addition, six dose-range studies were finished (ADD 03046, ADD 54001, ADD 40037, ADD 09004, ADD 17014, ADD 51006).

Proposed Course of Contract: This contract ended on February 28, 1983, but was extended until June 29, 1983, in order to complete ongoing work. A new RFP was written and advertised. A TMR reviewed 18 proposals. A new contract was initiated September 1983.

Publications: None

CONTRACT NARRATIVE
Convulsive, Developmental, and Neuromuscular Disorders Program
Epilepsy Branch
October 1, 1982--September 30, 1983

UCLA (N01-NS-0-2332)

Title: Comprehensive Epilepsy Program

Contractor's Project Director: Antonio Delgado-Escueta, M.D.

Date Contract Initiated: June 30, 1980

Current Annual Level: $1,263,000

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 urban geographic area.

Methods Employed: The contractor is conducting clinical and laboratory research in the diagnosis, treatment, prognosis, and prevention of epilepsy. The 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, the 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, rehabilitative, psychological, vocational, educational, and social services.

Major Findings: The investigators are exploring basic mechanisms of history of the disease, new methods of diagnosis and treatment, and the special problem of minority persons with epilepsy who reside in a large urban area.

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. The contract is 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: The contract underwent technical merit review during FY 1983 for funding of the -04 and -05 years.

Publications: Anderson V.E., Chern M.M., Schwanebeck E. Multiplex families and the problem of heterogeneity. In Genetic Research Strategies for Psychiatry, Gershon E.S., et al. (Eds.) Boxwood Press, pp. 341-351, 1981.

Bajorek J.G., Lee R. J., Catlin D.H., Lomax P. Effects of B-endorphin on experimentally induced seizures in mice. Proc. Wes. Pharmacol. Soc, 24: 315-317, 1981.

Bajorek J.G., Lomax P. Modulation of spontaneous seizures in the Mongolian gerbil: Effect of B-endorphin. Peptides 3: 83-86, 1982.

Bocash W.D., Cornford E.M., Oldendorf W.B. A correlation between lipid partition coefficients and transintegumental uptakes of nonelectrolytes in Schistosoma mansoni. Exp. Parasitol. 52:396-403, 1981.

Braun L.D., Cornford E.M., Oldendorf W.H. Newborn rabbit blood brain barrier is selectively permeable and differs substantially from the adult. J. Neurochem. 33:439-445. Jan. 1980.

Brown W. J., Mitchell A.G., Babb T. L., Crandall P.H. Structural and physiologic studies in experimentally induced epilepsy. Exp. Neurol. 69:543-562, 1980.

Cornford E.M., Oldendorf W.H. Blood brain barrier permeability to amines and amine precursors. Mosnaim A.D. and Wolf M.E. (Eds.) Chapter 2 in Noncatecholic Phenylethylamines, Modern Pharmacology-Toxicology Series, Volume 12, pp. 21-52. Marcel Dekker, Inc. New York. 1980.

Cornford E.M., Bocash W.D., Oldendorf W. H. Transintegumental glucose uptake in Schistosomatium douthitti. J. Neurochem. 36:1758-1765. 1981.

Cornford E.M., Huot M.E. Glucose transfer from male to female schistosomes. Science 213:1269-1271, 1981.

Cornford E.M. Correlation between lipid partition coefficients and the transintegumental uptake in Schistosoma japonicum. J. Membr. Biol. 64:396-403, 1982.

Cornford E.M. Differential uptake of 3-O methyl glucose in paired and unpaired Schistosomes. In Nuclear Techniques in the Study of Parasitic Infections, International Atomic Energy Agency, Vienna, Austria, pp.497-502, 1982.

Cornford E.M., Braun L.D., Oldendorf W.H., Hill M.A. Comparison of lipid mediated blood-brain-barrier permeability in the newborn and adult brain. Amer. J. Physiol. 243: C161-C168, 1982.

Cornford E.M., Braun L.D., Oldendorf W.H. Age-related alterations in blood-brain-barrier penetration of diphenylhydantoin. Adv. Epileptology, Akimoto H., Kazamatsuri H., Seino M., and Ward A.A. (Eds.) Raven Press, New York, 1982. pp. 285-288 .

Cornford E.M., Huot M.E., Diep C.P., Rowley G.A. Protein, glycogen, and water content in Schistosomes. J. Parasitol, 68, 1010-1020, 1982.

Cornford E.M. Blood-brain barrier permeability to anticonvulsant drugs. In Workshop on the Metabolism of Antiepileptic Drugs. Raven Press, New York, 1983 (In Press).

Cramer J.A., Smith D.D., Mattson R. H., Delgado-Escueta A.V., Collins J.F. A method for the qualification for the evaluation of antiepileptic drug therapy. Neurology January, 1983 (In Press).

Crane P.D., Braun L.D., Cornford E.M., Nyerges A.M., Oldendorf W.H. Cerebral cortical glucose utilization in the conscious rat: Evidence for a circadian rhythm. J. Neurochem. 34: 1700-1706, 1980.

Crane P.D., Pardridge W.M., Braun L.D., Nyerges A.M., Oldendorf W.H. The interaction of transport and metabolism on brain glucose utilization: A reevaluation of the Limmpe constant. J. Neurochem. 36: 1601-1604, 1981.

Cummings J. L., Syndulko K., Golberg Z., Treiman D.M. Palinopsia reconsidered. Neurology, 32: 444-447, 1982.

Delgado-Escueta A.V. The synapse in epilepsy. Chapter 6 in Mechanisms of Antiepileptic Drugs. Glasser G., Woodbury D., Penry J.K. (Eds.) Raven Press, New York, 1980.

Delgado-Escueta A.V. Phenytoin: Biochemical membrane studies. Chapter 20 in Mechanisms of Antiepileptic Drugs. Glaser G., Woodbury D., Penry J.K. (Eds.) Raven Press, New York. 1980.

Delgado-Escueta A.V., Davidson D., Victor S. The effects of seizures on calcium transport within synaptosomes. J. Neurochem. 34(5): 1140-1148, 1980.

Delgado-Escueta A.V., Mattson R.H., Goldensohn E.S., et al. The nature of aggression during epileptic seizures. New Eng. J. Med. 305: 711-716, Sept. 17, 1981.

Delgado-Escueta A. V., Wasterlain C., Treiman D.M., Porter R.J. Status Epilepticus: Mechanisms of Brain Damage and Treatment. Raven Press, New York, 1983.

Delgado-Escueta A.V., Horan M. The effects of seizures on ion transport and membrane protein phosphorylation. In Status Epilepticus: Mechanisms of Brain Damage and Treatment. Delgado-Escueta A.V., Wasterlain C., Treiman D.M., Porter R.J. (Eds.) Raven Press, New York 1982.

Delgado-Escueta A.V., Treiman D.M., Bacsal F.E. Phenotypic variations of seizures in adolescents and adults. In Genetic Basis of the Epilepsies. Anderson V.E., Penry J.K., Hauser W. A., Sing C.S. (Eds.) Raven Press, New York. pp 49-81. 1982.

Delgado-Escueta A.V., Bacsal F.E., Treiman D.M. Complex partial seizures on the CCTV-EEG: A study of 691 seizures in 79 patients. Ann. Neurol. 11: 292-300, 1982.

Delgado-Escueta A.V., Treiman D.M., Walsh, G.O. The Treatable epilepsies: I. Medical and surgical management. New Eng. J. Med. 308 (25) p. 1508-14, 1983 (In Press).

Delgado-Escueta A. V., Bajorek J.G. Status epilepticus: Mechanisms of brain damage and rational management. Epilepsia, 23 (Suppl. 1): S29-S41, Raven Press, New York, 1982.

Delgado-Escueta A.V., Walsh G.O. The selection process for surgery of intractable complex partial seizures: Surface EEG and depth electrography. In Epilepsy (Proceedings of the Association for Research in Nervous and Mental Diseases ARNMD). Research Publications Vol. 61 1983, Raven Press, Ward, Arthur A., Jr. (Ed.)

Delgado-Escueta A.V. Treatment of epilepsy in adolescents and adults. In Conn H.H. (Ed.) Current Therapy, 1983.

Diaz J., Shields W.D. Effects of dipropylacetate on brain development. Annals of Neurology, 10: 465-468, November 1981.

Ehrlich B.E., Diamond J.M., Braun L.D., Cornford E.M., Oldendorf W.H. Effects of lithium on blood-brain barrier transport of neurotransmitter precursors, choline, tyrosine and tryptophan. Brain Res. 193: 604-607, July 1980.

Fando J.L., Wasterlain C.G. A simple, reproducible cell-free system for measuring brain protein synthesis. Neurochem. Res. 5: 197-207, 1980.

Frydman M., Greenberg D.A., Mohandas T.K., Kaback M.M. Comparison of fetal and maternal chromosome polymorphisms: Applications in prenatal diagnosis. Prenatal Diagnosis 2: 25-31, 1982.

Goldberg M.A. Phenobarbital binding. In Glaser G., et al. (Eds.) Antiepileptic Drugs, Mechanisms of Action Chapter 30 Raven press, 1980.

Goldberg M.A., Todoroff T. Brain binding of anticonvulsants: Carbamazepine and valproic acid. Neurology 30:826. 1980.

Goldberg M.A., Eterobarb: Absorption, distribution, biotransformation and excretion. Chapter 72 in Antiepileptic Drugs, Second Edition. Woodbury D., Penry J.K., Pippenger C.E. (Eds.), Raven Press, (In Press).

Goldberg M.A., Merritt H.H. The Pharmacology of Phenytoin. Memorial Volume. Yawr M. (Ed.) Raven Press (In Press).

Goldberg M.A., McIntyre H.B., Barbiturates in the treatment of status epilepticus. In Wasterlain C., (Eds.): Status Epilepticus. Raven Press, 1982.

Greenberg D.A., Kaback M.M. Estimation of the frequency of hexosaminidase: A variant alleles in the American Jewish population. Am. J. Hum. Genet. 34: 444-451, 1982.

Grisar T., Franck G., Schoffeniels E. Glial control of neuronal excitability in mammals. II. Enzymatic evidence: Two molecular forms of the (Na^+, K^+) -ATPase in brain. Neurochemistry International, 2: 311-320, 1980.

Grisar T., Franck G. Effects of Changing K^+ Ion on rat cerebal cortex slices in vitro. A study during development. J. Neurochem. 36/5: 1853-1857, 1981.

Grisar T., Franck G., Delgado-Escueta A.V. Na^+, K^+ ATPase of bulk isolated glial cells, perikaryons and synaptosomes in the epileptogenic foci. Chapter 35 in Status Epilepticus; Mechanisms of Brain Damage and Treatment. Delgado-Escueta A.V., Wasterlain C.G., Treiman D.M., Porter R.J. (Eds.), Raven Press, New York, 1982.

Grisar T., Franck G., Delgado-Escueta A.V. (Na^+, K^+)-ATPase within neurons and glia in the generation of seizures in status epilepticus. In Status Epilepticus: Mechanisms of Brain Damage and Rational Management. Delgado-Escueta A.V., Wasterlain C.G., Treiman D.M., Porter R.J. (Eds.), Raven Press, New York, 1983.

Halgren E., Squires N.K., Wilson C.L., Rohrbaugh J.W., Babb T.L., Crandall P.H. Endogenous Potentials Generated in the Human Hippocampal Formation and Amygdala by Infrequent Events. Science 210: 803-805, 1980.

Halgren E. The Amygdala Contributon to Memory and Emotion: Current Studies in Humans. In Ben-Ari Y. (Ed.): The Amygdaloid Complex, Amsterdam pp. 395-408. 1981.

Halgren E. Mental phenomena induced by stimulation in the limbic system. Human Neurobiology 1. pp. 251-260, 1983.

Halgren E., Wilson C.L., Squires N.K., Engel J., Walter R.D., Crandall P.H. Dynamics of the human hippocampal contribution to memory. In W. Siefert (Ed.): The molecular, cellular and behavioral neurobiology of the hippocampus (In press).

Halgren E., Squires N.K., Wilson C.L., Crandall P.H. Brain generators of evoked potentials: The late (endogenous) components. Bull. L.A. Neurol. Soc. (In Press).

Hargittai P., Agoston D., Nagy A. Comparative biochemical and biophysical studies on rat brain synptosomes. FEBS Lett 137: 37-70, 1982.

Hodge S.E., Greenberg D.A., Rotter J.I., Lange K.L. Second order approximation of ascertainment probabilities. Biometrics, 36: 27-33.,1980.

Imagawa D.T., Howard E.B., Van Pelt L.F., Ryan CC.P., Bui H.D., Shapshak P. Isolation of canine distempervirus from dogs with chronic neurological diseases. Proc. Soc. Exp. Biol. and Med. 164: 355-362, 1980.

Jurez G., Lund G. Seizure clinics and comprehensive care. Urban Health. 11: 46, March 1982.

Lee J.L. Personal and professional characteristics of staff nurses. Amer. J. Nursing 82: 81, 1982.

Lewis C.E. Enhancing self-reliance and self-care while increasing access to primary care. Monograph, Agency for International Development, November 1980.

Lewis C.E. Interdisciplinary health services research : A physicians' perspective. In Contemporary Health Service, Johnson A., Grusky O., Raven B. (Eds.), Auburn House Publishing Co., Boston. pp. 255-264, 1982.

Lewis C.E. Nurse practitioners and the physicians surplus. In Nursing in the 1980's: crises, opportunities, challenges. Aiken, Linda (Eds.), Lippincott, 1982.

Lewis C.E. Decision making related to health: when could/should children act responsible? In Development Factors in Competence to Consent, Plenum Publishing. (In Press).

Lewis C.E., Lewis M.A. Provider behavior, the utilization of health services provider satisfaction and social-medical policy. Man and Medicine, Vol. 5, No. 1980.

Lewis C.E., Lewis M. Determinants of children's health-related beliefs and behaviors. Family and Community Health, February 1982.

Lewis C.E., Lewis M.A. Teaching children self-care: A countercultural proposal. Learning for life, a conference on future of health education in British Columbia. Government of Canada, Federal Health Promotion Directorate, 1982.

Lewis C.E., Lewis M.A. Children's health-related decision making. Health Education Quarterly, 9: 129-141, Summer/Fall 1980.

Lewis M.A. Managing nurse practitioners in ambulatory care: What are the issues? J. Nursing Admin., X:7, 11-17, July 1980.

Locke G. Febrile seizures. Urban health, Vol. 11, No. 2, March 1982.

Lock G., Biggers S., Brown L. Post-traumatic epilepsy. Urban Health, Vol. 11, No. 5, June 1982.

Lund G., Mittan R. The urban epilepsy program at King/Drew Medical Center. Urban Health, 11(1): 30-32, 1982.

Maldonado H., Joseph J.P., Schlag J. Type of eye movements evoked by thalamic electrical microstimulation in the alert cat. Exp. Neurol. 70: 613-625, 1980.

Masdeu J.D., Fine M., Shewmon D.A., Placios E., Naidu S. Post-ischemic hypervascularity of the infant brain: Differential diagnosis on computed tomography. Amer. J. Neuroradiol. 3: 501-504, 1982.

Mattson R. H., Delgado-Escueta A.V., Cramer J. A., Smith D.B., Collins J.F. A design for the prospective evaluation of the efficacy and toxicity of antiepileptic drugs. Neurology, 33, Suppl. 1, 14-25, 1983. (In Press).

McIntyre H.B., Goldberg A. The knowledgeable use of the EEG in seizure disorders. In Seminars in Neurology, Vol. 1, No. 2, pp. 77-80, 1981.

McIntyre H.B., Firemark H.M., Comez M. Computer Analyzed EEG in Amphetamine-responsive hyperactive children. Psychiatric Research, 4: 189-197, 1981.

Mittan R., Wasterlain C., Locke G. Fear of seizures. In Advances in Epilepsy-1981, Akimoto H. Kazamatsuri H., Seino M. (Eds.), Raven Press, New York, 1982.

Mittan R., Locke G. Fear of seizures: Epilepsy's forgotten symptom. Urban Health, 11(1): 40-41. 1982.

Moorthy G., Locke G. Cerebral seizures and alcohol abuse. Urban Health, Vol. 11, No. 2, pp. 45-46, March 1982.

Mouritzen D.A., Bajorek J.G., Lomax P. Hippocampal neuron density and seizures in the Mongolian gerbil. Epilepsia, 22: 1981.

Nagy A., Bock E. Synaptin in acetylcholine and catecholamine-containing synaptic vesicle fractions from brain cortex. Biochem. Biophys. Acta. 600:103-107, 1980.

Nagy A., Shuster T.A., Rosenberg M.D. Adenosine triphosphatase activity at the external surface of synaptosomes. J. Neurochem., 40: 226-234, 1983.

Oldendorf W. H., Cornford M.E., Brown W.J. Some unique ultrastructural characteristics of rat brain capillaries. In Cerebral Microcirculation and Metabolism. Cervos-Navarro J., Fritschka E. (Eds.), Raven Press, New York, pp. 9-15, 1981.

Oldendorf W.H. Notes and impressions from meeting: Clinical nuclear magnetic resonance (NMR) imaging symposium; Winston-Salem, North Carolina, October 1-3, 1981. J. Computer Assisted Tomography, 6(2): 429-430, April 1982.

Oldendorf W. H., Pardridge W. M., Braun L.D., Crane P.D. Measurement of cerebral glucose utilization using washout after carotid injection in the rat. J. Neurochem. 38(5): 1413-1418, 1982.

Pardridge W. M., Frank H.J.L., Cornford E. M., Braun L.D., Crane P.D., Oldendorf W.H. Neuropeptides and blood-brain barrier. In Neurosecretion and brain peptides: Implication for brain function and neurological disease., Martin J.B., Reichlin S., Bick K.L. (Eds.) Raven Press, New York. Adv. Biochem. Psychopharmacol., Vol. 28, 321-328, 1981.

Pardridge W. M., Crane P.D., Mietus L. J., Oldendorf W.H. Kinetics of regional blood-brain barrier transport and brain phosphorylation of glucose and 2-deoxyglucose in the barbiturate-anesthetized rat. J. Neurochem. 38(2): 560-568, February 1982.

Pardridge W.M., Crane P.D., Mietus L. J., Oldendorf W.H. Nomogram for 2-deoxyglucose lumped constant for rat brain cortex. J. Cerebral Blood Flow Metabol., 2: 197-202, 1982.

Percy A.K., Byrd S.E., Locke G. Cerebral cysticercosis. Pediatrics, Vol. 66, No. 6, pp. 967-970, December 1980.

Shewmon D.A. The use of electroencephalography in the newborn period. Proc. Hines/Loyola Med. Ctr. Conf. Neurol., 37: 592-594, 1980.

Shewmon D.A., Masdeu J.C. Delayed radiation necrosis of the brain contralateral to original tumor. Arch Neurol. 37: 592-594, 1980.

Shewmon D.A., Fine M., Masdeu J.C., Palacios E. Post-ischemic hypervascularity of infancy. A stage in the evolution of ischemic brain damage with characteristic CT scan. Ann. Neurol. 9: 358-365, 1981.

Shields W.D., Feldman R.C. Serum CK-BB isoenzyme in pre-term infants with periventricular hemorrhage. Pediatr. 100: 464-468, 1982.

Smith D.B., Cramer J.A., Delgado-Escueta A.V., Mattson R.H. Historical perspective on the choice of antiepileptic drugs. Neurology, p. 2-7.

Squires, N.K., Halgren E., Wilson C.L., Crandall P.H. Human endogenous limbic potentials: Cross-modality and depth/surface comparisons in epileptic subjects. In Tutorials in ERP Research/N: Endogenous Components, Gaillard A.W.K., Ritter W. (Eds.), Amsterdam: North-Holland. (In Press).

de la Sota A., Lewis M.A., Lewis C.E. Actions for health: Decision-making and self-reliance activities for healthful living. Addison-Wesley Publishing Co., Menlo Park, California, 1980.

de la Sota A., Herfindahl L., Lee J., Clark M., Treiman D.M. Circle of decisions: A new epilepsy patient education program. In Advances in Epileptology-1981, Akimoto H., Kazamatsuri H., Seino M. (Eds.) New York, Raven Press pp. 471-473, 1982.

Treiman D.M., Delgado-Escueta A.V. Status epilepticus. In Critical Care of Neurological and Neurosurgical Emergencies. Thompson R.A. (Ed.) Raven Press, New York, pp. 53-99, 1980.

Treiman D.M. Seizures types and causes of epilepsy. Seminars in Neurology, 1: 65-75, 1981.

Treiman D.M., Delgado-Escueta A.V., Bacsal F.E. Sub-classification of Complex Partial Seizures by CCTV-EEG analysis. In Advances in Epileptology-1981, Akimoto H., Kazamatsuri H. Seino M. (Eds.) Raven Press, New York, pp. 61-64, 1982.

Treiman D.M., Delgado-Escueta A.V. Complex partial seizures. In Status Epilepticus; Mechanisms of Brain Damage and Treatment, Delgado-Escueta A.V., Wasterlain C., Treiman D.M., Porter R.J. (Eds.) Raven Press, New York, 1982.

Treiman D.M. General principles of treatment: Responsive and intractable status in adults. In Status Epilepticus: Mechanisms of Brain Damage and Treatment, Delgado-Escueta A.V., Wasterlain C., Treiman D.M., Porter R.J. (Eds.) Raven Press, New York, 1982.

Treiman D.M. Treatment of status epilepticus. Seizure Disorder Update, Vol. 5, Warner-Lambert Company, 1982.

Treiman-Tokunow J., Treiman D.M. New media approaches for public awareness about epilepsy. In Advances in Epileptology-1981, Akimoto H., Kazamatsuri H., Seino M. (Eds.) Raven Press, New York pp. 467-470, 1982.

Tourtellotte W.W., Shorr R.J. Cerebrospinal fluid. In Neurological Surgery, Vol. I Second Edition. Youmans J.R. (Ed.), W.B. Saunders, Co., Philadelphia, pp. 423-486, 1982.

Twombly D., Delgado-Escueta A.V. Cellular and membrane events in the mirror focus. In Secondary Epileptogenesis. Mayersdorf A., and Schmidt R. (Eds.) Raven Press, New York, 1982.

Walter D.O. Computer analysis of the synthesizing brain. In Recent Advances in EEG and EMG Data Processing, Yamaguchi N., Fujisawa J. (Eds.), pp. 3-15. Amsterdam:Elsevier, 1981.

Weil M.L. Contributing editor (Seizure disorders of infants and children). In Primary Care of Seizure Disorders. McIntyre H.B. (Ed.) Butterworth, 1982.

Whitlock C.A., Ziegler S.F., Treiman L.J., Stafford J.L., Wittee O.N. Differentiation of cloned populations of immature B cells after transformation with Abbelson Murine leukemia virus. Cell, 32(3): 903-11, March 1983.

Winchell H.S., Horst W.D., Braun L.D., Oldendorf W.H., Hattner R., Parker H. N-isopropyl (I-123) p-Idodamphetamine: Single-pass brain uptake and washout, binding to brain synaptosomes; and localization in dog and monkey brain. J. Nucl. Med., 21: 947-952, October 1980.

Wilson C.L., Babb T.L., Halgren E., Crandall P.H. Visual receptive fields and response properties of neurons in human temporal lobe and visual pathways. Brain Jun; 106 (Pt 2): 473-502, 1983.

CONTRACT NARRATIVE
Convulsive, Developmental, and Neuromuscular Disorders Program
Epilepsy Branch
October 1, 1982--September 30, 1983

UNIVERSITY OF MINNESOTA (N01-NS-0-2341)

Title: Epilepsy Information Transfer

Contractor's Project Director: Robert Gumnit, M.D.

Date Contract Initiated: September 30, 1980

Current Annual Level: $113,000

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 in-house 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.

Major Findings: The investigators are exploring new ways of transferring information more rapidly to physicians, allied health personnel, and concerned lay people.

Methods Employed: This project began September 30, 1980. The contractor is developing, testing, and implementing a broad program of 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 programs and materials in cooperation with appropriate lay organizations; to develop, test, and implement educational programs for the patient; and to 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. This may point the way to future areas of research.

Proposed Course of Contract: This project expired September 29, 1983.

Publications:

Annegers, J.F., Kurland, L.T., and Hauser, W.A. Teratogenicity of anticonvulsant drugs. In J.F. Annegers, L.T. Kurland and W.A. Hauser (Eds.), Epilepsy. New York, Raven Press, 1983, pp. 239-248.

Hauser, W.A. The Role of Epidemiology in the design of clinical trials of anticonvulsant drugs. Epilepsia 23 (Suppl. 1), pp. S43-S52, New York: Raven Press, 1982.

Hauser, W.A. Status epilepticus: Frequency, etiology and neurological sequelae. In A.V. Delgado-Escueta, C.G. Wasterlain, D.M. Treiman and R. J. Porter (Eds.), Advances in Neurology. New York: Raven Press, 1983, pp. 3-14.

Hauser, W.A., J.F. Annegers, and Anderson, V.E. Epidemiology and the genetics of epilepsy. In Arthur A. Ward, Jr., J. Kiffin Penry, and Dominick P. Purpura (Eds.), Epilepsy. New York: Raven Press, 1983, pp. 267-294.

CONTRACT NARRATIVE
Convulsive, Developmental, and Neuromuscular Disorders Program
Epilepsy Branch
October 1, 1982--September 30, 1983

UNIVERSITY OF UTAH (NO1-NS-0-2335)

Title: Early Pharmacologic Evaluation of Anticonvulsant Drugs

Contractor's Project Director: Ewart Swinyard, Ph.D.

Date Contract Initiated: November 1, 1980

Current Annual Level: $526,000

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 inital evaluation. These parameters are determined at the 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. During this last year, in vitro receptor binding studies on selected compounds have been added to Phase 5. Phases 6 and 7 are carried out in rats. In Phase 6, the median effective anticonvulsant dose (ED_{50}) amd 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, as well as the effect of candidate compounds on drug metabolism.

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, 1982, over 1,000 compounds were screened for Phase I. Of those compounds which had completed all seven phases, eight were selected as possible candidates for the pharmacology/toxicology project.

Proposed Course of Contract: The contract ends October 31, 1983; a Technical Merit Review was held in summer 1983.

Publications: None

CONTRACT NARRATIVE
Convulsive, Developmental, and Neuromuscular Disorders Program
Epilepsy Branch
October 1, 1982--September 30, 1983

UNIVERSITY OF WASHINGTON (NO1-NS-1-2349)

Title: Study of Experimental Anticonvulsant Drugs in Primates

Date Contract Initiated: February 16, 1981

Contractor's Project Director: Joan Lockard, Ph.D.

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 FY 80 and resulted in the award of the present three-year contract to the University of Washington. A series of studies were performed during the present year. These were assay and pharmacokinetic studies, efficacy studies, and metabolic studies involving several anticonvulsants. The results will aid in making decisions regarding appropriate clinical trials.

Major Findings: Under the present contract, the following studies have been performed or started: 1.) The kinetic studies of ADD 35002 were completed. 2.) The efficacy pilot protocol for this compound was designed and implemented with a finding of little or no efficacy in the primate model. 3.) Preliminary dosing studies of ADD 40016 have been completed. 4.) Kinetic studies of ADD 03055 have begun. 5.) Six monkeys have beeen selected to be used in an efficacy pilot study of ADD 03055.

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. Such studies serve as an incentive to the pharmaceutical industry in developing new drugs.

Proposed Course of Contract: The contract will expire January 15, 1984.

Publications: Levy, R.H., Viswanathan, C.T. and Lockard. J.S. Time-dependent kinetics VIII: Diurnal oscillations in valproic acid disposition following single dose administration in Rhesus monkey. Journal of Phar. Sciences, (In press).

Lockhard, J.S., and Levy, R.H. Experimental quantification and evaluation of anticonvulsant drugs in the primate model. In D.M. Woodbury, J.L. Penry and C.E. Pippenger (Eds.) Antiepileptic Drugs. New York: Raven Press, 1982, pp.127-140.

Lockard, J.S. and Levy, R.H. Valproate nonreversibility: Dosing procedures critical? Workshop on Antieplieptic Drugs, Phoenix, Arizona 1982, Raven Press, (In press).

Lockard, J.S., Levy, R.H., Ducharme, L.L and Congdon, W.C. EEG quantification of drug level effects in monkey model of partial Epilepsy. In W.A. Cobb, Buser, P.A. and Okuma, T. (Eds.): Kyoto Symposia (EEG Suppl. No. 36), 1982, pp. 487-503.

Lockard, J.S., Levy, R. H., Kirkevold, B.C. and Ludwick, B.T. A monkey model for drug interaction: Exemplified by valproate and phenytoin. In H. Akimota, H. Kazamatsuri, M. Seino, and A. Ward (Eds.): Advances in Epileptology, 1981. New York: Raven Press, 1982, pp. 301-306.

CONTRACT NARRATIVE
Convulsive, Developmental, Neuromuscular Disorders Program
Epilepsy Branch
October 1, 1982--September 30, 1983

UNIVERSITY OF MINNESOTA (N01-NS-1-2371); UNIVERSITY OF VIRGINIA (N01-NS-1-2367)

Title: Progabide in Partial Seizures

Contractor's Project Directors: Ilo Leppik, M.D.; Fritz Dreifuss, M.D.

Date Contracts Initiated: September 30, 1981

Current Annual Level: $84,000 (University of Minnesota $10,000; Univeristy of Virginia $74,000)

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. Nine patients were admitted this year to the Phase II study at the University of Virginia; 13 were admitted at the University of Minnesota. 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: As of September 30, 1983, 16 patients completed the Phase II study at the University of Virginia, and 20 completed the Phase II study at the University of Minnesota. Contracts are to be completed as of one month following the date of completion of the final patient.

Publications: None

CONTRACT NARRATIVE
Convulsive, Developmental, and Neuromuscular Disorders Program
Epilepsy Branch
October 1, 1982--September 30, 1983

UNIVERSITY OF WASHINGTON (NO1-NS-1-2368)

Title: Late Phase I Study of ADD 03055 in Patients with Partial Seizures

Contractor's Project Director: Alan Wilensky, M.D.

Date Contract Initiated: September 29, 1982

Current Annual Level: $83,000

Objective: To assess the pharmacokinetics and toxicity of ADD 03055 in patients with partial seizures, to obtain preliminary evidence of efficacy of ADD 03055 as an add-on medication, and to obtain information concerning enzyme induction, accelerated metabolism, and antagonism or inhibition of the other antiepileptic drugs concomitantly administered.

Methods Employed: The study is an open, unblinded pilot study of two groups of four patients with uncontrolled partial seizures. One group received only phenytoin in addition to ADD 03055, while the other group received only carbamazepine in addition to ADD 03055. The duration of the treatment period was one month. Preliminary data regarding the pharmacokinetics, tolerability, and metabolism were obtained.

Major Findings: There has been a dramatic and uniform drug interaction of ADD 03055 with phenytoin. Drug toxicity has been limited to that which would be expected from phenytoin intoxication.

Significance to Biomedical Research and the Program of the Institute: This study is intended to provide data to determine in part whether to proceed to definitive efficacy studies in patients with partial seizures. The study is also intended to promote methodological advances in the area of antiepileptic drug testing.

Proposed Course: This contract expired on September 29, 1983.

Publications: None

CONTRACT NARRATIVE
Convulsive, Developmental, and Neuromuscular Disorders Programs
Epilepsy Branch
October 1, 1982,--September 30, 1983

UNIVERSITY OF WASHINGTON (N01-NS-1-2368); UNVERSITY OF CALIFORNIA, LOS ANGELES (N01-NS-1-2377)

Title: ADD 35002 (Nafimidone) in Partial Seizures

Contractor's Project Directors: Alan Wilensky, M.D.; David Treiman, M.D.

Date Contracts Initiated: September 30, 1982

Current Annual Level: $82,000 (University of Washington $48,000; University of California, Los Angeles $34,000)

Objectives: To characterize the efficacy and safety of a new antiepileptic agent in the treatment of refractory partial seizures.

Methods Employed: The main study covered by these contracts is a randomized, double-blind, two-period crossover study comparing nafimidone 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 being preceded by a pilot study of six patients at each of the two centers.

Major Findings: The pilot study is currently being completed. There has been a dramatic and uniform drug interaction of nafimidone with both phenytoin (PHT) and carbamazepine (CBZ). Plasma levels of both these concomitant drugs have increased. The exact mechanism for this interaction is under investigation. Drug toxicity has been limited to only that which would be expected from PHT or CBZ intoxication.

Proposed Course: Contract is intended to provide for data on 30 completed patients by August 30, 1985, at the University of Washington and 30 completed patients by August 30, 1985, at the University of California, Los Angeles.

Publications: None

CONTRACT NARRATIVE
Convulsive, Developmental, and Neuromuscular Disorders Program
Epilepsy Branch
October 1, 1982--September 30, 1983

UNIVERSITY OF UTAH (NO1-NS-1-2347); UNIVERSITY OF MICHIGAN (NO1-NS-1-2363)

Title: ADD 40016 (Fluzinimide) in Partial Seizures

Contractors' Project Directors: Jack Madsen, M.D.; J. Chris Sackellares, M.D.

Date Contracts Initiated: September 30, 1982

Current Annual Level: $159,000 (University of Utah $7,000; University of Michigan $152,000)

Objectives: To characterize the efficacy and safety of a new antiepileptic agent 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 Fluzinimide with placebo when given as an add-on medication to patients with partial seizures refractory to therapy with the 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 on micro-computers with recording of data on floppy disks programmed in advance at the Epilepsy Branch. The main study is being preceded by a pilot study of six patients at each of the two centers.

Major Findings: The pilot study is currently being completed. One patient has had a complete cessation of his seizures and continues to do well on Fluzinimide. There have been two losses to the study due to idiosyncratic rashes presumably due to the drug. The original maximum drug dosage has been reduced and the daily dosing interval increased. Both of these changes occurred as a result of patient toxicity which mainly consisted of gastrointestinal distress and dizziness.

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, 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 methodolgical advances in the area of antiepileptic clinical drug testing.

Proposed Course: Contract is intended to provide for data on 25 completed patients by August 30, 1985, at the University of Utah and 25 completed patients by August 30, 1984, at the University of Michigan. Contracts are completed as of one month following the date of completion of the final patient.

Publications: None

CONTRACT NARRATIVE
Convulsive, Developmental, and Neuromuscular Disorders Program
Epilepsy Branch
October 1, 1982,--September 30, 1983

MANDEX (N01-NS-3-2354)

Title: Survey of Antiepileptic Drug Usage

Contractor's Project Director: Leonard Greenberg, M.A.

Date Contract Initiated: September 15, 1983

Current Annual Level: $114,000

Objective: To estimate the prescribing and dispensing of drugs by chemical name for epileptic seizures in the United States, to estimate the types and frequencies of seizures for which the drugs are prescribed, and to estimate the number of patients receiving specific antiepileptic drugs alone or in combination.

Methods Employed: A request for proposals was issued during the year and resulted in the award of an eight-month contract. The following tasks will be performed as part of the contract: (1) pharmacy-based drug dispensing survey, and (2) patient-based survey of drug usage linked to diagnoses of epilepsy by seizure types per reporting period.

Significance to Biomedical Research and the Program of the Institute: Study findings will be used to estimate the impact of marketing of drugs made available by the Antiepileptic Drug Development Program of the NINCDS, to confirm priorities with respect to seizure types, and to estimate the appropriateness of drugs prescribed for specific seizure types.

Proposed Course of Contract: The contract will expire May 31, 1984.

Publications: None

CONTRACT NARRATIVE
Convulsive, Developmental, and Neuromuscular Disorders Program
Epilepsy Branch
October 1, 1982--September 30, 1983

University of Minnesota (NO1-NS-1-2371); University of Virginia (NO1-NS-1-2367)

Title: ADD 03055 in Partial Seizures

Contractor's Project Director: Ilo Leppik, M.D.; Fritz Dreifuss, M.D.

Dates Contracts Initiated: September 30, 1983

Current Annual Level: $264,000 (University of Minnesota $132,000; University of Virginia $132,000)

Objectives: To characterize the efficacy and safety of a new anticonvulsant in the treatment of refractory partial seizures.

Methods Employed: The main study which will be covered by these contracts are a randomized, double-blind, two-period crossover study comparing ADD 03055 with placebo when given as an add-on medication to patients with partial seizures refractory to therapy with one standard drug, phenytoin or carbamazepine. Contracts will be 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 will be preceded by a pilot study of four patients at each of the two centers.

Major Findings: Study to begin September 30, 1983.

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, 1986, at Center A, and 30 completed patients by August 30, 1986, at Center B. Contracts are completed as of one month following the date of completion of the final contract.

Publications: None

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01-NS-02511-03 EB

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Development of Analytical Methods of Analysis for Potential Anticonvulsants

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Harvey J. Kupferberg Pharmacologist CDNDP NINCDS

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Epilepsy Branch

SECTION

Preclinical Pharmacology Section

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.02	.01	.01

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Extraction procedures for a variety of anticonvulsant compounds were developed using a preferential solvents system theory. The final methods were found to be suitable for a variety of both animal and humans. This project has been completed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01-NS-02512-03 EB

PERIOD COVERED: October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Inhibition of Microsomal Primidone Metabolism by Phenytoin

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)

Maria C. Porro Pharmacologist CDNDP NINCDS

COOPERATING UNITS *(if any)*

None

LAB/BRANCH: Epilepsy Branch

SECTION: Preclinical Pharmacology Section

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

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.02	.01	.01

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects
  - ☐ (a1) Minors
  - ☐ (a2) Interviews
- ☐ (b) Human tissues
- ☒ (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been terminated.

PHS 6040 (Rev. 1/83) GPO 895-100

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01-NS-02539-02 EB

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

HPLC Analysis for Progabide and Major Metabolite in Plasma of Epileptic Patients

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Wayne Yonekawa Pharmacologist CDNDP NINCDS

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Epilepsy Branch

SECTION

Preclinical Pharmacology Section

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.02	.01	.01

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A high pressure liquid chromatographic (HPLC) method, which uses an electrochemical detector for specificity and sensitivity, was developed to simultaneously quantitate both progabide and its major metabolite in plasma of epileptic patients receiving the orally administered drug. Both drug and metabolite can be quantitated to levels of 10 ng/ml of plasma. The assay is presently being used in the NINCDS clinical studies. This project has been completed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01-NS-02540-02 EB

PERIOD COVERED: October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

In Vitro Inhibition of Phenytoin Metabolism by Carbamazepine

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)

Harvey J. Kupferberg Pharmacologist CDNDP NINCDS

COOPERATING UNITS *(if any)*

None

LAB/BRANCH: Epilepsy Branch

SECTION: Preclinical Pharmacology Section

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

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.02	.01	.01

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been terminated.

PHS 6040 (Rev. 1/83) GPO 895-100

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01-NS-02581-01 EB

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Antiepileptic Drug Interactions in a Microsomal System

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Izet M. Kapetanovic Pharmacologist CDNDP NINCDS

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Epilepsy Branch

SECTION

Preclinical Pharmacology Section

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.0	0.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Drug-drug interactions are not uncommon during antiepileptic therapy. These interactions constitute a clinical problem due to a relatively narrow therapeutic index for antiepileptic drugs. Many of these interactions are a result of altered drug metabolism. Most recently, unexpected drug-drug interactions were observed during Antiepileptic Drug Development clinical trials for two promising candidate antiepileptic drugs, (ADD 35002, ADD 03055). When either of these drugs was added to the existing phenytoin and carbamazepine therapy, a dramatic rise in plasma levels of the latter drugs was observed. An in vitro rat hepatic microsomal system is being used to study interactions between antiepileptic drugs. A standard Michaelis-Menten approach is being applied to define kinetic parameters Km, Vmax, and Ki for microsomal metabolism of anticonvulsants. This in vitro system is being used to elucidate mechanisms behind these interactions. It may also be potentially useful as a screening procedure for predicting the interactions.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01-NS-02582-01 EB

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

HPLC Assay for ADD 35002 and ADD 03055 in Plasma of Epileptic Patients

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Wayne Yonekawa Pharmacologist CDNDP NINCDS

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Epilepsy Branch

SECTION

Preclinical Pharmacology Section

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
.02	.01	.01

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Analytical methods for the quantitation of drugs in biological matrices were needed for the various phases in the development of two potential anticonvulsant agents, ADD 35002 and ADD 03055. Both these compounds are currently undergoing NINCDS-sponsored clinical efficacy trials, and plasma level measurements are integral to these studies. These measurements had to have specificity and sensitivity in order to quantitate these agents not only for efficacy studies, but also for pharmacokinetic and toxicologic investigation. The methodology involved examination of the physical and chemical characteristics of each compound in order to determine the most suitable chromatographic and detection procedures. It was also noted that ADD 35002 had a metabolite which required quantitation. It was found that all compounds could be analyzed on high performance liquid chromatographs with reverse phase C-18 columns. The dectection employed variable wavelength UV and fluorescence monitoring. The sensitivity limits were found to be less than 6 ug/ml for ADD 03055 and less than 10 ng/ml for ADD 35002. Linearity was excellent throughout the range needed for analysis. The final methods were found to be suitable for a variety of both animal and human investigation. This project has been completed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01-NS-02583-01 EB

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Effect of Potassium and Pentylenetetrazole on Hippocampal Discharges in Vitro

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Salvatore Piredda Visiting Associate CDNDP NINCDS

COOPERATING UNITS *(if any)*

Laboratory of Neurochemistry, NINCDS

LAB/BRANCH

Epilepsy Branch

SECTION

Preclinical Pharmacology Section

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.0	1.0	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The usefulness of the mouse hippocampal slice preparation and the study of the role of potassium in the generation of ictal activity was the subject of this research. The methods included studying the effects of various extracellular potassium (K^+) concentrations on spontaneous or pentylenetetrazole (PTZ) induced discharges both in the presence and absence of anticonvulsant agents. Standard techniques were used to obtain extracellular recordings in the CA_3 region of hippocampal slices from NIH general purpose mice. The K^+ concentration in the medium was adjusted with potassium chloride, and the effects of these manipulations were noted. It was found that no spontaneous bursts occurred at low K^+ (3.25 mM), but spontaneous discharges were observed in a majority of the slices at higher K^+ (9.25 mM). PTZ-induced discharges occurred in slices at concentrations ranging from 100 ug/ml to 200 ug/ml and were found to be positively correlated to increasing K^+ concentration. This PTZ-induced activity was reversible. These observations substantiate the putative role of potassium in the generation of ictal episodes and the modulation of hippocampal neuronal excitability. Preliminary investigations using anticonvulsant agents show that clonazepam abolished the bursting elicited with PTZ whereas phenytoin did not. These results are similar to those obtained using the in vivo pentylenetetrazole subcutaneous threshold test in mice.

ANNUAL REPORT

October 1, 1982 through September 30, 1983

Developmental Neurology Branch, CDNDP
National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

Table of Contents (cont'd)

ANNUAL REPORT
For Period October 1, 1982 through September 30, 1983
Developmental Neurology Branch
Convulsive, Developmental, and Neuromuscular 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 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 approximately 182 grants classified as Disorders of Early Life, a major disorder category within the extramural grant program. The DNB also has responsibility for grants classified as Neuromuscular Disorders, another major category which includes 163 active grants.

Four program announcements have been issued for DNB initiatives in Reye's syndrome, neonatal brain disorders, neural tube defects, and the neurophysiology of learning disorders. Two other program announcements in the areas of autism and the phakomatoses are under development. A 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 continued this fiscal year.

The DNB has continued effort during this fiscal year to complete the objectives of the Comprehensive Plan for Analysis and Interpretation of NINCDS Collaborative Perinatal Project (NCPP) Data. During the year a total of 12 papers were published or are in press. A major report on neuropathology analysis has been published (Gilles, F.H., Leviton, A., and Dooling, E.C.: The Developing Human Brain: Growth and Epidemiologic Neuropathology. Boston, MA., John Wright-PSG Inc. 1983, pp 349). As the NINCDS will soon complete its use of the Collaborative Perinatal Project data, a contract was awarded for the production of a "User's Guide" to the NCPP data to facilitate the long-term management of the microfilm and computer tape files as a national data resource.

The DNB, representing the NINCDS, is jointly sponsoring with the National Institute of Child Health and Human Development a report on "Prenatal and Perinatal Factors Associated with Brain Disorders". The report will be written in conjunction with selected consultants and will be jointly issued by the two Institutes.

Other significant 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. 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 for 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. Several subprojects of these program projects have been submitted as R01 research grant applications; one has been awarded.

Current activities on febrile seizures include several chapters for books and professional journals. 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 published as a monograph in 1983. 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 contractor is studying 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. Patient accrual began in November, 1982, and this study is now underway.

A study of the EEG as a predictor of febrile seizures has begun in Yugoslavia in pursuance of another of the recommendations of the Consensus Development Conference.

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. All five regression analyses have been run, and a final concatenated file is in preparation. Cerebral palsy at 7 years is found more frequently in boys than girls, and among whites than blacks. Twelve percent 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. The interaction of obstetric events and Apgar scores as risk factors for cerebral palsy has been studied, and a paper submitted for

publication. Associated handicaps have been investigated in children with 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, and analyses for the monograph are nearing completion.

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 the 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. A manuscript on neonatal seizures in the NCPP, prepared under contract, has been published, and a paper on the antecedents of neonatal seizures is in preparation. 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 in progress. Mothers with non-eclamptic 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 published. Papers on the age of onset of seizures in young children, and on the risk of recurrence of seizures, were presented at national professional meetings; the former has been submitted for publication, the latter is in manuscript. A paper on seizures soon after immunizations was published, and the Section presented information relating to this topic to the Redbook Committee of the American Academy of Pediatrics, at the invitation of the chairman of that committee.

A study of febrile seizures, a major focus of the convulsive disorders area, has been completed save for analyses of antecedents, which are now in progress. Of 1706 children with febrile seizures followed to the age of 7 years, 3% had at least one nonfebrile seizure by the age of seven years. 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.

Among other relevant activities of the Section were teaching an Epilepsy Course at the annual meeting of the American Academy of Neurology, and

appointment of the Section Head to the Professional Advisory Board of the Epilepsy Foundation of America.

Section on Mental Retardation and Learning Disorders

Twenty-nine research grant applications have been received in response to the program announcement on brain dysfunction in disorders of learning issued in January of 1982. Excluding the three unassigned applications to be considered at the October 1983 Council, 13 applications were assigned primarily to NINCDS, 12 to NICHD and one to NIMH. Of these 26 applications, one was funded by NINCDS and one by NICHD, two have been deferred and 13 disapproved. The remaining nine were approved but not funded. It is anticipated that a number of these applications will be amended and re-submitted. The Section assists in the development, review, and monitoring of these research grant applications. The Section also admininsters some 50 research grants that are primarily in the area of developmental neurobiology.

Section members have participated in meetings of the Society for Research in Child Development and the Interagency Child Development Research Group, and have presented papers at meetings of the Behavior Genetics Association, the American Psychological Association, and the Association for Children with Learning Disabilities. At the latter meeting, the Section Chief assisted in organizing a symposium and presented an invited address.

In the study of mental retardation in the NCPP, it was found that the prevalence 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 severe retardation include Down's syndrome, major CNS malformations, neonatal seizures, clinical signs of perinatal hypoxia and maternal seizures in pregnancy. Among severely retarded children with unknown etiology, non-CNS malformations, peripheral nerve abnormalities, signs of hypoxia, and maternal urinary tract infection during pregnancy were important perinatal risk factors. Mild mental retardation is also associated with some perinatal complications but less strongly than with indices of maternal intelligence, education, and socioeconomic status of the family. Physical and mental development of the retarded children are discussed as are familial patterns of mental retardation and an analysis of drugs taken during pregnancy. A monograph is in preparation.

A small subgroup of the retarded children who did not have any major neurological abnormalities were given the diagnosis of autism. The autistic children were compared with IQ-matched controls to determine if any early characteristics were useful in identifying these children. No eight month measures and only one four year behavioral rating, response to directions, differentiated the autistic and other retarded children. The autistic group did, however, differ behaviorally from normal controls as early as eight months.

In the learning disabilities area, behavioral, physical, and family characteristics of children with average IQ scores and below average school

achievement, approximately 3% of the NCPP population, were identified. Cognitive deficits and behavior problems in the preschool period were associated with low achievement at age seven. Socioeconomic status (SES) and family structure were stronger predictors of low achievement than were indices of perinatal status or later physical development. 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 with early developmental problems more readily identified in girls than boys. A monograph has been submitted for publication.

A study of the relationship between obstetric medication and physical and cognitive development through age seven has been completed. Subjects were full-term infants of mothers with uncomplicated pregnancies and deliveries from two hospitals in the NCPP. Pharmacological agents studied 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 neurological examination. Significant associations between outcomes and drugs were examined in multiple logistic regression analyses with other risk factors included. The results suggest that inhalants and oxytocin are associated with deficits in early motor development. Administration of scopolamine and secobarbital is related to respiratory difficulties in the newborn, and inhalants, scopolamine, and secobarbital are associated with palpable liver at 4 months. At later ages, scopolamine and oxytocin are associated with lower scores on some cognitive and achievement tests. This is one of the few investigations of possible long-term effects of obstetric medications.

Section on Birth Defects and Genetic Disorders

The Section is responsible for the administration of some 100 research grants in the areas of developmental neurology and genetic disorders, particularly those of metabolic origin.

A fair proportion of the research grant activity has been in neural tube defects, for which a program announcement was issued in December, 1981. The research goals of this program are to gain 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 susceptibility, and prevention and treatment of neural tube defects. In response to the Program Announcement, 17 applications have been received dealing with various aspects of neural tube defects, and three of these have been funded. The Section has also focused attention on another group of neurogenetic disorders about which little is known, the phakomatoses. A program announcement for research in basic mechanisms as well as clinical aspects of the phakomatoses has been prepared and is expected to be issued shortly.

Among other activities is a compilation and updating of a comprehensive list of all known heritable disorders of the nervous system which to date numbers about 1,000.

The Section Chief participated in the 10th World Federation of Neurology Workshop on Huntington's Chorea, workshops on idiopathic scoliosis, the use of vitamins for prevention of neural tube defects, and a US-Japan workshop on Inborn Errors of Metabolism, and represented the Institute as a member of the "Ad Hoc NIH Work Group on Inherited Metabolic Disorders". He attended several scientific meetings and was a speaker at a meeting of the Society for Research into Hydrocephalus and Spina Bifida. He also lectured to medical students at George Washington University School of Medicine as an Associate Clinical Professor of Neurology, and to various other scientific and lay groups, participated in the NIH Medical Genetic Conferences, and engaged in genetic counseling.

The Section continues its research activities to complete the analysis of NCPP congenital malformations data. Nine parts of the 11-part analysis have been completed, two are still in progress. The analysis of minor and multiple malformations, and their classification, is being carried out in collaboration with investigators from the University of Hawaii, who assisted in the design, the selection of variables and the production of preliminary tabulations. The analysis of the 7-year malformations, now in its final stages, updates the findings of 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 between 1 and 7 years. Only 7.5% were completely lost to the study. 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. About 12% of children who did not have malformations at 1 year have developed a malformation between 1 and 7 years. About 5% of children had malformations at both 1 and 7 years.

Epidemiologic analysis of neural tube defects has shown that increased risk for these defects is associated with maternal diabetes and organic heart disease, diuretics, antihistamines, sulfonamides and thyroxin taken during the first trimester, and a short immediately previous pregnancy interval. But siblings of children with certain major malformations do not appear to be at increased risk for neural tube defects, nor are siblings of children with neural tube defects at increased risk for other major malformations.

The incidence of pyloric stenosis in the NCPP data and in additional data collected from the Baltimore area was found to be about 2 per 1000 live births, and much higher in males than in females, and in whites than in non-whites. Rh incompatibility and birth order (higher incidence in first-born) are significantly associated with pyloric stenosis, but maternal age, birthweight and length of gestation are not.

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

The Section Chief has developed a Program Announcement on "The Neurobiology of Autism" and obtained from NICHD and NIMH counterpart extramural program administrators approval to issue this announcement solely from NINCDS-DNB. A Workshop on Research Definitions for Disorders of the Autistic Spectrum was held on September 29-30, 1983. The Section administered approximately 22 grants.

The liaison of the Section Chief with Clinical Center groups has expanded. In addition to continued close interaction with the Unit on Childhood Mental Illness (studies of Autistic Adults, Obsessive-Compulsive Adolescents, and Attentionally-Deficient Children), there have been periodic consultations with the Interinstitute Genetics Group, where Fragile X-autism, Downs-mosaic-Asperger, and behaviorally-disordered neurofibromatosis cases have been discussed.

Activities with voluntary organizations this year have included (1) two lectures given in February, 1983, for the Asssociation for Children and Adults with Learning Disabilities, one of which was sponsored jointly by the National Society for Autistic Children; and (2) a lecture presentation at the Symposium of the National Neurofibromatosis Foundation, May, 1983. Organizational liaison activities have included (1) the initial meeting of the Stallone Fund for Autism research (hosted by United Way, April, 1983); and (2) representation of autism at a luncheon for several voluntary groups concerned with developmental research given in conjunction with the ACLD meeting in February 1983.

In addition, the Section Chief has made, between December 1982 and May 1983, eight lecture presentations, all on program relevant topics (autism, Asperger's Syndrome, disorders of social cognition, and attention deficit disorder) to professional audiences, with resultant inquiries about research training and submissions of many preliminary or draft research proposals.

Collaborative Perinatal Section

The Unit for Data Collection is responsible for maintaining the NINCDS Collaborative Perinatal Project files in accordance with a system designed to facilitate data retrieval. During the fiscal year, major efforts were concentrated on supplying data to DNB professional staff and outside investigators, providing research assistance to on-going studies and monitoring the creation of the Collaborative Perinatal Project User's Guide. This Unit is also responsible for monitoring the digital computer storage of medical data collected by NCPP, the automated bibliography of all NCPP publications, and the cost accounting of computer funds spent by the Branch. The entire NCPP file has been sent to the Federal Records Center and the Master Copy and one work copy of NCPP microfilm file and the computer tape files have been transferred to National Underground Storage, Inc. in Boyers, PA. Research assistance via computer tapes, computer printouts or access to microfilm was provided to 9 in-house investigators and 10 outside investigators.

III. NEUROMUSCULAR DISORDERS

The Program supports 163 active grants for research in basic nerve and muscle function and dysfunction with special emphasis on Muscular Dystrophy, Myasthenia Gravis and Peripheral Neuropathies. 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 60% of the funds (102 grants) are devoted to basic research on nerves, muscles and their interactions. 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.

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 1983, 26 grants were awarded in the Muscular Dystrophy sub-program, including one program project.

Myasthenia Gravis

Myasthenia Gravis 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 1983, there were 17 active grants.

Peripheral Neuropathies

The peripheral neuropathies are common and are serious health problems often associated with prolonged morbidity. The majority of the affected population is diabetic. 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 CDNDP 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 1983, 15 regular grants and one clinical research center program project were awarded.

IV. 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 applications. This program announcement was cosponsored by three other institutes. There have been nine grants funded by NINCDS since 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, mitochondrial function, metabolic patterns during disease, and muscle metabolism after recovery.

The Chief, DNB was appointed by the Assistant Secretary for Health, DHHS, to serve on the PHS Reye's Syndrome Task Force. The charge to this task force is to develop a study of the possible association of salicylate to the development of Reye's Syndrome and to assess and report PHS research activities on Reye's Syndrome to the Assistant Secretary.

V. 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 new annual and ternary reports, prepared and submitted to the NIH Privacy Act Coordinator; (4) reviewing requests for access to and amendment of grant records; (5) attending orientation sessions regarding changing regulations in implementation of the Act; and (6) revising NINCDS System Notices as required.

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.

CONTRACT NARRATIVE
Developmental Neurology Branch, CDNDP, NINCDS
Office of the Chief
October 1, 1982 through September 30, 1983

BATTELLE MEMORIAL INSTITUTE (NO1-NS-2-2311)

TITLE: Creation of a User's Guide to the Data of the Collaborative Perinatal Project.

Contractor's Project Director: Anthony R. Olsen

Current Annual Level: $ 248,495.00

Objectives: The specific objective of this contract is to produce a comprehensive User's Guide to the data of the NINCDS Collaborative Perinatal Project which will allow effective, efficient, and independent use of the data by researchers unfamiliar with the data and its use. A second major aim is to produce, as part of the User's Guide, sufficient documentation of tape files to meet the requirement of independent data use of the National Archives.

Major Findings: First drafts of all elements of the User's Guide have been produced. A complete second draft was reviewed by DNB staff, and independent field testing began in August of 1983.

Significance to the Program: The NCPP data is a national resource for biomedical and behavioral research and is being used to address current research issues. Successful completion of the contract will release the DNB from long-term commitment to service functions regarding assistance to new researchers.

Course of Contract: One Year. The User's Guide, in suitable form for publication, was completed by September 30, 1983.

Publications: Not applicable.

CONTRACT NARRATIVE
Developmental Neurology Branch, CDNDP, NINCDS
Office of the Chief
October 1, 1982 through September 30, 1983

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: $320,261.00

Objectives: The University of Washington is conducting 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. Subjects are being entered into the study and followed during FY83. 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, CDNDP, NINCDS
Office of the Chief
October 1, 1982 through September 30, 1983

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 neurpathology 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 evaluation 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 published.

Course of Contract: June 1, 1973 through December 31, 1976. The contract is terminated.

Publications: Gilles, F.H., Leviton, A., and Dooling, E.C.: The Developing Human Brain: Growth and Epidemiologic Neuropathology. Littleton MA: John Wright-PSG, Inc., 1983, 349 pp.

CONTRACT NARRATIVE
Developmental Neurology Branch, CDNDP, NINCDS
Office of the Chief
October 1, 1982 through September 30, 1983

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).

Major Findings: Findings are reflected in approximately 34 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 continued to analyze and publish NCPP data with support from sources other than the NINCDS. The contract file was officially closed this Fiscal Year.

CONTRACT NARRATIVE
Developmental Neurology Branch, CDNDP, NINCDS
Office of the Chief
October 1, 1982 through September 30, 1983

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 final 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 children from the NINCDS Collaborative Perinatal Project (NCPP).

Major Findings: Findings are reflected in approximately 52 publications to date. A comprehensive report in book form is now in press.

Significance to the Program: Findings have prompted a great deal of discussion and editorial comment within the pediatric community, and have established leads to further reseaarch.

Course of Contract: The contract terminated July 31, 1979. Dr. Naeye continued to analyze and publish NCPP data with support from an NINCDS grant (1 RO1 NS 16403-01). The contract file was officially closed this Fiscal Year.

CONTRACT NARRATIVE
Developmental Neurology Branch, CDNDP, NINCDS
Office of the Chief
October 1, 1982 through September 30, 1983

CHILDREN'S HOSPITAL MEDICAL CENTER, BOSTON, MASSACHUSETTS: (NO1-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 was allowed for completion of the final report in the form of a monograph suitable for publication.

Publications: None

CONTRACT NARRATIVE
Developmental Neurology Branch, CDNDP, NINCDS
Office of the Chief
October 1, 1982 through September 30 1983

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: The monograph is now being written. Eleven of twenty-two chapters have been received.

Course of Contract: March 13, 1978 through March 13, 1983.

Publications: None

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02058-11 DNB

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Convulsive Disorders Data Analysis Group

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
PI: K.B. Nelson Pediatric Neurologist 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 *(Use standard unreduced type. Do not exceed the space provided.)*

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. A paper on seizures occurring soon after immunization procedures has been published, and a paper on age of onset of seizures in young children has been submitted for publication. A paper on risk of recurrence after a single nonfebrile seizure has been presented at a national professional meeting, and a manuscript is in preparation. A paper on obstetric conditions and Apgar scores as risk factors for nonfebrile seizure disorders has been submitted for publication.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02059-11 DNB

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Cerebral Palsy Data Analysis Group

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
PI: K. B. Nelson Pediatric Neurologist 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:
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 *(Use standard unreduced type. Do not exceed the space provided.)*

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. A study on obstetric factors as antecedents of cerebral palsy has been submitted for publication. An investigation of the antecedents of a major risk factor for cerebral palsy, very low birthweight, is in preparation. Analysis of forward risks for cerebral palsy based upon maternal and obstetric factors is being programmed, and multivariate analysis is nearing completion.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02060-11 DNB

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Birthweight-Gestational Age

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

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 *(Use standard unreduced type. Do not exceed the space provided.)*

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 relations 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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02106-10 DNB

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Developmental Factors Associated with Mental Retardation

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
PI: S. H. Broman Chief, MRLDS 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 *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this study is to identify antecedents of severe and mild mental retardation in a large population of children studied from the prenatal period to age 7. The prevalence 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 severe retardation include Down's syndrome, major CNS malformations, neonatal seizures, clinical signs of perinatal hypoxia and maternal seizures in pregnancy. Among severely retarded children with unknown etiology, non-CNS malformations, peripheral nerve abnormalities, signs of hypoxia, and maternal urinary tract infection during pregnancy were important perinatal risk factors. Mild mental retardation is also associated with some perinatal complications, but less strongly than with indices of maternal intelligence, education, and socioeconomic status of the family. Physical and mental development of the retarded children are discussed as are familial patterns of mental retardation and an analysis of drugs taken during pregnancy. A monograph is in preparation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02107-10 DNB

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Study of Visual Abnormalities in the NINCDS Collaborative Perinatal Project

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

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 Science; 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:
0.0	0.0	0.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project included 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; and case studies of the blind children. Basic data analysis was completed and computer-generated tables are on file. The project is terminated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02108 - 10 DNB

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Developmental Factors Associated with Learning Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
PI: S. H. Broman Chief, MRLDS 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 *(Use standard unreduced type. Do not exceed the space provided.)*

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. Cognitive deficits and behavior problems in the preschool period were associated with low achievement at age seven. Socioeconomic status (SES) and family structure were stronger predictors of low achievement than were indices of perinatal status or later physical development. 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 with early developmental problems more readily identified in girls than boys. A monograph has been submitted for publication.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02109-10 DNB

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Comprehensive Analysis of the NCPP Data on Congenital Malformations

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

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 *(Use standard unreduced type. Do not exceed the space provided.)*

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 significance 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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02112-10 DNB

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neonatal Hyperbilirubinemia

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

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 *(Use standard unreduced type. Do not exceed the space provided.)*

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 included 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. Findings were generally negative. No publication is anticipated. The project is terminated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02169 - 09 DNB

PERIOD COVERED: October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Obstetrical Medication and Development in Infancy and Early Childhood

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

PI: S.H. Broman 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 *(Use standard unreduced type. Do not exceed the space provided.)*

This study investigated relationships between obstetric medication and physical and cognitive development through age seven. Subjects were full term infants of mothers with uncomplicated pregnancies and deliveries from two hospitals in the NCPP. Pharmacological agents studied 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 neurological examination. Significant associations between outcomes and drugs were examined in multiple logistic regression analyses with other risk factors included. The results suggest that inhalants and oxytocin are associated with deficits in early motor development. Administration of scopolamine and secobarbital is related to respiratory difficulties in the newborn, and inhalant anesthetics, scopolamine, and secobarbital are associated with palpable liver at 4 months. At later ages, scopolamine and oxytocin are associated with lower scores on some cognitive and achievement tests. This is one of the few investigations of possible long-term effects of obstetric medications.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02171-09 DNB

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Compendium of Heritable Disorders of the Nervous System

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
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)
- [X] (a) Human subjects
  - [X] (a1) Minors
  - [ ] (a2) Interviews
- [X] (b) Human tissues
- [ ] (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02234-08 DNB

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Febrile Seizures Study

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

PI: K.B. Nelson Pediatric Neurologist 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 *(Use standard unreduced type. Do not exceed the space provided.)*

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. Several invited chapters have been published on this topic. 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 has begun 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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02332-06 DNB

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Analysis of NCPP Twin Data

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
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)
- [X] (a) Human subjects
  - [X] (a1) Minors
  - [ ] (a2) Interviews
- [X] (b) Human tissues
- [ ] (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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.

Annual Report

October 1, 1982 through September 30, 1983

Demyelinating, Atrophic and Dementing Disorders Program

TABLE OF CONTENTS

ADMINISTRATIVE SUMMARY

The Demyelinating, Atrophic and Dementing Disorders Program was officially established at the beginning of FY83 as a result of the reorganization of the Neurological Disorders Program. Dr. Carl M. Leventhal was Acting Director of the Program from its creation in May 1982, until he was assigned to the Office of Science and Technology Policy in May 1983. Dr. Emanuel M. Stadlan is the present Acting Director of the Program.

Dr. Nancy Wexler, Health Scientist Administrator for the Huntington's Disease portfolio, resigned her position in June 1983 to become Vice President of the Hereditary Disease Foundation. Previously she had been the Executive Director of the Commission for the Control of Huntington's Disease and Its Consequences.

New Initiatives

During FY 83 the Demyelinating, Atrophic and Dementing Disorders Program and the Convulsive, Developmental and Neuromuscular Disorders Program implemented some of the recommendations generated by the Veterinary Advisory Workshop which convened in August 1982. The primary recommendations of the workshop were: to sensitize the veterinary community to the need for naturally occurring animal models of human neurological diseases, and to encourage interaction between veterinary neurologists and the general neuroscience community. The NINCDS held a workshop at the annual meeting of the American Veterinary Medical Association in New York, July 1983, during which these interests were shared with veterinarians. An NINCDS booth was also on display throughout the meeting. In addition, all veterinary neurologists were invited by the Society for Neuroscience and the American Academy of Neurology to join and participate in their activities.

The Program, in conjunction with the Office of Biometry and Field Studies, and with the cooperation of the Intramural and all Extramural Programs, convened a meeting of pain experts to determine whether there has been sufficient progress in the methodologies for the assessment and measurement of pain to justify a symposium on this subject. The response of the participants was enthusiastic and a conference proposal on this topic is anticipated.

Program staff undertook a follow up study of Huntington's Disease in Venezuela with a group of extramural scientists in the spring of 1983. Additional neurological examinations were performed and recorded on film, tissues and fluids were collected and stored in three different repositories, and follow-up genetic and epidemiologic data were gathered and submitted to the HD registry in Indiana. Program staff also collaborated with Registry personnel in the preparation of a monograph on the Epidemiology of Huntington's Disease, which was sponsored by the office of Biometry and Field Studies.

Research Summary

Introduction: The Demyelinating, Atrophic and Dementing Disorders Program encourages and supports basic and clinical research relating to the understanding, diagnosis, treatment and prevention of a variety of neurological disorders including Huntington's disease, Alzheimer's disease, Parkinson's

disease, multiple sclerosis, amyotrophic lateral sclerosis, ataxia, pain, and chronic infections of the nervous system. Research activities include studies of the physiology, biochemistry, pharmacology, anatomy, pathology, genetics and epidemiology of these and related conditions in humans and in animal models.

A few of the highlights will be mentioned. NINCDS grantees have demonstrated the feasibility of grafting nervous and non-nervous system tissues to animal brains. Grafted cells remain viable and functional. The development of this technique has important therapeutic implication for disorders resulting from the failure of focal collections of neurons to secrete neurotransmitters, as, for example, in Parkinson's disease.

Ongoing studies continue to strongly support the earlier observations regarding the consistent degeneration of the cholinergic neurons of the nucleus basalis and septal nuclei in the brains of Alzheimer's disease patients. Various exploratory and therapeutic efforts to selectively replenish acetylcholine in order to retard the loss of cognitive function and improve memory are underway.

The search for the location of the Huntington's disease gene and identification of its products is proceeding well because of the available tissues provided by Venezuelan and other HD patients and the utilization of new technology.

Research in multiple sclerosis continues to support the observation that the immune system is somehow deranged in this disorder, but its role in the etiology has yet to be elucidated. Five investigator-initiated randomized clinical trials of immunomodulating agents in MS patients are presently underway in the United States, supported by NINCDS.

DEGENERATIVE NEUROLOGICAL DISORDERS OF ADULT LIFE

The Program supports research in the neurobiology of degenerative disorders such as Parkinson's disease, Huntington's disease, Alzheimer's disease, and tardive dyskinesia. The Parkinson's disease portfolio consists of 30 grants, including 2 Clinical Research Centers, and costs nearly $4 million. The Huntington's disease program has 12 grants, including 2 Centers, at a cost of $2 million. Research on Alzheimer's disease and other dementias of aging is gradually increasing. Currently 20 grants, including one Center, are active, at a cost of $2 million. Other projects include work on the structural and functional alterations of the normal and aging nervous system (10 grants, $750,000) and tardive dyskinesia (6 grants, $400,000). The total program contains 78 active research grants totaling $9,100,000.

Parkinson's Disease

Parkinson's disease (paralysis agitans), the most frequent form of parkinsonism, is a common illness of middle life. One-half million people in the United States or about 1% of the population over age 50, are affected by this disease.

The primary cause of Parkinson's disease remains a mystery. The dopamine containing neurons in the substantia nigra invariably degenerate. The clinical signs of the disease, tremor, rigidity, and bradykinesia, become progressively more severe with time. Many patients suffer gradually diminishing intellectual faculties. The symptoms of Parkinsonism can also result from the administration of neuroleptics, as sequelae of certain encephalitides, and from a variety of diseases and intoxications.

The majority of studies 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 brain dopamine deficiency in Parkinson's disease led to subsequent understanding of the neurochemistry and pharmacology in other brain disorders.

Clinical Studies

With the subsiding of the excitement which followed the discovery that dopamine replacement therapy ameliorates symptoms of Parkinson's disease, it has become increasingly apparent that additional or other treatment modalities are necessary for some patients. Unpleasant side effects and an erratic effectiveness of the treatment, known as the "on-off" phenomenon, have pushed scientists to seek new agents. Many of these compounds act in concert with L-dopa to increase its potency while others mimic its action.

New compounds will hopefully be added to the armamentarium currently available for treating parkinsonism. Investigators at New York University, dedicated to discovering novel treatments for parkinsonism, have had some success using dopamine agonists such as bromocriptine and lergotrile. Both drugs were effective in relieving tremor of parkinsonian patients and monkeys with lesions in the thalamus. However, lergotrile was shown to be hepatotoxic. Several

ergoline derivatives were evaluated for their dopamine agonist activity in animals, but only two drugs, pergolide and lisuride, were shown to be potent dopamine agonists and long acting agents in experimental animal models. Preliminary clinical trials with pergolide are encouraging. Studies suggest that pergolide has a high affinity for pre- and postsynaptic dopamine receptors, while its partial ergoline analogue has a high affinity for the presynaptic, but not for the postsynaptic dopamine receptors. The data also suggest that dopamine synthesis in vitro and in vivo may be regulated by different presynaptic dopamine receptors.

At the Mount Sinai School of Medicine new drugs being tested include: L-Deprenyl-MAO-B Inhibitor, ergoline derivatives, citicoline, L-Threo-3,4, dihydroxylphenyl Serine, and L-5-Hydroytyptophan. L-Deprenyl enhances the central effects of levodopa and is useful as an adjunctive agent in controlling the oscillations in symptoms in patients receiving long term L-dopa treatment. Since L-Deprenyl also causes release and blocks re-uptake of monamines in the brain and inhibits release of acetylcholine, this group is studying its usefulness when administered without levodopa in the early phases of parkinsonism. Preliminary studies show that it has equivalent but more sustained effects than amantadine and lacks some of the latter's toxicity. The ergoline derivatives are being studied for their efficacy in patients experiencing untoward side effects in the course of Sinemet therapy. Preliminary studies indicate that pergolide has fewer side effects than bromocriptine and is effective in relatively low doses.

Centers

At the University of Colorado "Center for the Study of Basal Ganglia Disorders and Neurotransmitter Function," 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 multi-disciplinary study of neurotransmitters and neuromodulators in the central nervous system with major emphasis on the basal ganglia and the nigrostriatal dopamine pathway. Tyrosine hydroxylase from rat pheochromocytoma has been purified to homogeneity and its physical and kinetic properties have been characterized. Adrenal and pheochromocytoma tyrosine hydroxylase appears to exist in two kinetically distinct forms. There also is present in rat striatum an enzyme which activates tyrosine hydroxylase by a mechanism which requires ATP and Mg++, but which is neither Ca++ nor cyclic AMP dependent. Fetal rat striatal tyrosine hydroxylase appears to be less susceptible to activation by cyclic AMP-dependent protein kinase than the adult enzyme. Apparently, the neural circuits required to mediate the in vivo activation of striatal tyrosine hydroxylase consequent to postsynaptic dopamine receptor blockade are not fully developed until 10-12 days postnatally. An immunocytochemical procedure was developed for localizing tyrosine hydroxylase in brain and peripheral tissues. These studies are providing new information on the physiological regulation of dopamine synthesis.

This group has also made the interesting observation that brain tissues which are grafted to a host eye or brain remain viable and establish functional connections with the host brain or subsequent grafts. Moreover, chromaffin cells grafted to the brain alter their morphology, assume a neuronal appearance, and provide functional catecholamine input to host brain. New techniques are being developed to examine the effectiveness of these brain grafts.

Basic Science

The discovery of multiple receptor types for dopamine holds the promise for major advances in the development of better pharmacological tools to treat movement disorders such as parkinsonism and tardive dyskinesia. Over the last few years evidence has been obtained that both peripheral and central neurons have receptors located on their cell bodies and terminal varicosities which, when activated, lead to facilitation or inhibition of neurotransmission. One type of presynaptic receptor is the autoreceptor which is activated by the released transmitter or related analogues. The autoreceptor appears to play an important physiological role in the negative or positive feedback modulation of the release and/or synthesis of that specific transmitter. Although the precise physiological role of presynaptic receptors is still not clear, there is little doubt that such presynaptic receptors exist and offer the possibility for different types of pharmacological interventions. Moreover, they may play an important pathophysiological role in various neurological and psychiatric diseases.

Exploring this concept, an investigator at St. Louis University has found that dopamine autoreceptors are located on dopaminergic terminals of the nigrostriatal, mesolimbic and mesocortical neurons but not on the tubero-infundibular dopamine neurons. He also determined that the potency of various agonists for dopamine autoreceptors varies markedly in different regions of the CNS. The catecholamine agonists were more potent in inhibiting dopamine synthesis in the mesolimbic structures. On the other hand, apomorphine and epinine were less potent while dopamine was more potent in the medial basal hypothalamus. Chronic treatment with haloperidol results in supersensitivity of dopamine autoreceptor function. Data have also been obtained which suggest that there are distinct morphine and enkephalin receptors in the CNS which co-exist in an opioid-receptor complex. Work will continue in order to gain an understanding of pharmacological differences between autoreceptors and post synaptic receptors.

Recent studies have shown that a cholecystokinin-like peptide coexists in a subpopulation of midbrain dopamine-containing neurons. This peptide increases the activity of some, but not all, dopaminergic neurons. This suggests that cells in the dopamine rich areas of the mesencephalon can be characterized both on the basis of their content of peptide and/or catecholamine and of their responsiveness to cholecystokinin-like peptides.

Investigators at the Johns Hopkins University are utilizing electrophysiological and anatomical methods 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, and while neurons in key brain areas are monitored, they perform a limb movement. Microelectrode recording from and stimulation of the putamen revealed that neurons related to motor activity or somatosensory stimulation of the leg were located dorsolaterally, while those related to the face were located ventromedially. Neurons related to the arm were located in an intermediate position. Four different functional types of neurons were identified and their receptive fields were determined. The results also indicate that microstimulation of the putamen (but not of the caudate nucleus) of the waking primate is capable of producing

motor effects comparable to those elicited by microstimulation of the motor cortex. While it has been known for the last decade that neurons in the putamen are activated in relation to movements of specific body parts, this is the strongest evidence to date that such neurons may contribute directly to motor output rather than simply reflecting influences from motor cortex.

Huntington's Disease

Huntington's disease (HD) is a fatal hereditary degenerative disease of the brain resulting in uncontrollable abnormal movements 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 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 the patients. Treatment is at best 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 onset. The disease is characterized biochemically by reduced stores of GABA, glutamic acid decarboxylase (GAD), acetycholine (ACh), substance P, angiotensin II converting enzyme, and a 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.

Scientists supported by the NINCDS are investigating this disease from all possible aspects. Major emphasis is on the genetics of the disorder. Anatomical, biochemical and clinical studies are also being done. The investigation in Venezuela represents a hallmark in the history of HD studies.

Venezuela Project

A major project of the Program has been the study of a unique population of Huntington's disease families living on the shores of Lake Maracaibo. The original aim of this Project was to locate individuals homozygotic for the disease, that is inheriting the defective gene from both parents. The assumption was that examining persons with two abnormal genes might lead to major breakthroughs in understanding the defect involved as was the case for familial hypercholesterolemia, a hereditary heart disease.

In 1978 and 1979, the aims of the Venezuela Project were expanded in response to major breakthroughs in recombinant DNA technology which now permits specific genes to be localized on specific chromosomes. It now seems possible to locate the gene defective in Huntington's disease using as markers the small structural variations within the DNA of the gene. This approach requires tissue samples from a large number of genetically related people descended from a common ancestor, who transmitted the defective gene. The Venezuelan Huntington's disease community, which is probably the largest in the world, is ideal for this purpose. The ultimate goal of the Project is to identify, isolate, and clone the gene that causes Huntington's disease.

In 1979, a first trip to Venezuela was undertaken to conduct a feasibility study. In 1980, a contract for the Project was signed with the University of Zulia; and in March, 1980, the first of three month-long expeditions to the Lake Maracaibo region was undertaken.

The Venezuela Project has 3 major components: 1) the collection and documentation of the pedigree; 2) a clinical assessment of family members; and 3) collection of tissue samples from relevant individuals. The pedigree now contains more than 2,000 people and covers 8 generations. It has been said that the illness originated from a Spanish sailor named Antonio Russo Doria who jumped ship in the 1860's and left this legacy. Examination of the birth and death records showed that Antonio Russo Doria, a sailor from Spain, did indeed die in this region. It has not been possible to connect the descendents of Doria with members of the pedigree. Instead, the gene has been traced back to a woman living in a stilt village in Thisaica in the early 1800's. Whether the gene came from Spain, Columbia, or Venezuela remains a mystery.

One advantage of working with a pedigree this large is that there are special populations like twins which can provide additional research information. They have studied a pair of monozygotic twins concordant for HD and another fraternal set of very young twins.

In the pedigree there are seven unions between two affected individuals producing 29 offspring. Eighteen of these offspring have been intensively examined. Approximately one third have HD, another third have a normal neurological profile, although they are still quite young, and the remaining third have some minor neurological abnormalities. Thus far, no clinical entity which appears to be unique and, thus, clinically suggestive of homozygosity, has been observed. This may mean that a double dose of HD is lethal at conception, since an increased miscarriage history in any of these unions has not been observed. Alternatively, Huntington's disease may be a true dominant disorder so that the homozygotic form appears identical to the heterozygotic form. Once a gene marker is identified, it will be possible to recognize if any of these 18 individuals are homozygotes.

Over the last three years a standardized, quantitative neurological examination has been carried out on 230 individuals, including 57 Huntington's disease patients. Of these people 158 are 50% at risk or possible HD individuals, and 15 are 25% at risk. Most have been re-examined in subsequent years so that it is possible to measure the rate of progression. Interestingly, using the same scale of measurement the Venezuelan Huntington's disease patients seem to decline at the same rate or possibly slightly slower than patients on treatment in the United States. This indicates that the palliative therapies used do not alter the progress of the illness. The quantitative neurological examination assesses the entire spectrum of signs and a neuropsychological evaluation is also obtained on all patients. Some patients receive a more intensive psychiatric assessment.

The Huntington's Disease Roster in Indianapolis has computerized all pedigree information. They have also run conventional examinations on all samples collected in order to test for non-paternity, which has proved to be surprisingly low.

Tissue samples have been collected from 483 individuals to date. These samples are so superior for gene linkage work that in addition to using them to develop and screen for markers for Huntington's disease, they are excellent as general reference pedigrees for general gene mapping. Samples are available through the NIGMS Camden Cell Bank to investigators worldwide.

Genetic Studies

The goal of a number of laboratories supported by the NINCDS is to identify the chromosomal location of the Huntington's disease gene using recombinant DNA technology. One laboratory at Massachusetts General Hospital focuses both on development of new markers on human chromosomes and screening them against a large Huntington's disease pedigree. The ultimate goal is to apply this strategy to identify, isolate and clone the HD gene. In the past year, the laboratory has more than doubled the number of cell lines (from 270 to 574) derived from the Venezuelan Huntington's disease pedigree. In addition, cell samples have been obtained and collaborations were established with scientists in Wales who have access to several Welsh pedigrees. The diversity of pedigrees will provide assurance that the marker is linked to the HD gene itself and is not unique to a particular family.

Progress was also made in the generation of new markers on the human genome. Thirteen have been discovered by this laboratory. Six of the new probes were derived from the library of chromosome 21, while the others are scattered randomly throughout the genome and include representatives on chromosomes 3, 4, 5, and 10. This laboratory has also collected fourteen anonymous DNA probes from other investigators.

The markers developed by this laboratory, particularly on chromosome 21 or 19, will be of great use for studying other genetic disorders, in particular Down's syndrome and myotonic dystrophy. Localizing the Huntington's disease gene will be a major breakthrough in Huntington's research. Of course, there is a tremendous amount of work to be done in going from marker identification to isolating the mutant gene and identifying its product. A marker indicating the presence of the Huntington's disease gene would permit prenatal diagnosis and a definitive biochemical screen for the disease.

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. Kainic acid produces a selective degeneration of intrinsic striatal 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 the cortical-striatal glutamatergic pathways are interrupted.

At The Johns Hopkins University School of Medicine measurements are being made of the specificity of receptor binding of kainic acid and kainic acid-induced release of labeled neurotransmitters from slices of hippocampus, striatum, and cerebellum. Intact animal preparations are used to study 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. Considerable progress has been made in the characterization of excitatory acidic amino acid receptors using ligand-binding techniques. Preliminary data indicate the existence of a presynaptic receptor for kainate on putative glutamatergic neurons and the existence of endogenous peptides that interact with a high degree of specificity and high affinity with the glutamate receptor.

It has been speculated that the HD defect involves a dysfunction in the synthesis or degradation of a kainic acid-like substance. Scientists at the University of Tennessee have already begun to investigate the neurotoxic mechanism of an endogenous neuroexcitatory tryptophan metabolite, quinolinic acid. These studies have indicated that doses even as low as 10uM can induce prominent post-synaptic swelling and that post-synaptic elements appear to be the site of the initial toxic response. Studies are continuing on the steric requirements of the quinolinic acid molecule and on the location and concentration of the acid in the human brain.

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. To achieve these ends, the Hereditary Disease Foundation has held interdisciplinary workshops on Huntington's disease and other degenerative disorders. 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. Recent subjects included: the structure and function of the basal ganglia, brain gene expression, and excitotoxic models for HD.

Huntington's Disease Center

One of the most important 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 clinical 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.

In a recent study which has proven highly sensitive as an early diagnostic test, 243 sessions have been run on the protocol for assessing voluntary and involuntary movement, and include patients with Huntington's disease and individuals at risk for the disease, as well as patients with Alzheimer's disease, multi-infarct dementia, Parkinson's disease, and young adult and aged normal controls. Analyses of the involuntary movement data on the Huntington's disease, at-risk Huntington's disease and control groups have shown test-retest reliability coefficients ranging from .32 to .99, depending on task and group status. Validity analyses show that accelerometer scores are correlated

significantly with duration of illness, and approach significant associations with clinical ratings of chorea. The device, depending on the task, is capable of differentiating 65-100% affected from normal controls, and from 4-56% of those at risk.

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 complementary scientific investigations in participating institutions.

The Boston Center has discovered and substantiated a new finding in brain biochemistry in Huntington's disease. Increased levels of somatostatin in the neostriatum have been identified and the clinical and pathological implications of this finding are being explored. Cellular localization of other peptides, neurotransmitter-related enzymes, in post-mortem brain tissues is being pursued in several laboratories connected with the Boston Center Without Walls. Reliable staining methods in human post-mortem basal ganglia were formulated with antisera to leu-enkephalin, substance-P and somatostatin. Methods for staining cholecystokinin and serotonin are in progress. One hypothesis explaining the elevated somatostatin levels in HD brain may be the preferential survival of somatostatin containing afferent cells.

The clinical component of the Boston Center is collecting basic genetic, demographic, statistical, and psychosocial information. Three hundred and five individuals from 153 apparently unrelated families were evaluated over the course of the year. The social and psychological qualities of Huntington's disease were assessed by questionnaire. Although the literature has always purported that the suicide rate for Huntington's disease patients is high, the Boston Center has substantiating data for the first time. The period between the time that a person is at risk, but not definitely affected, with hope of escaping the disease, and the time that the patient is a confirmed gene carrier seems to be the most dangerous. Establishing a program of regular neurological examinations might alert medical professionals to impending signs of the illness and enable them to evaluate suicidal potential during this difficult time. These data regarding attitudes of at-risk individuals toward prediction and frequency of suicide are particularly important in view of a major project supported by the Center to find a DNA marker for the Huntington's disease gene. This marker would provide a means for diagnosing presymptomatic gene carriers, both prenatally and postnatally. Individuals at risk could be tested in order to definitely determine whether or not they carry the defective gene. The suicide risk among this presymptomatic group might be quite substantial.

Alzheimer's Disease and Other Dementias of Aging

The problem of the dementias in the United States has assumed alarming proportions. Lewis Thomas called Alzheimer's disease "the disease of the century" and Fred Plum called it "the plague of the future." At least two-thirds of elderly people with advancing dementia suffer from Alzheimer's disease (AD). The study of Alzheimer's disease has recently attracted numerous groups of investigators from many disciplines, ranging from sociology to molecular biology.

Much of the research supported by the NINCDS in this area seeks to clarify the structural and biochemical abnormalities which characterize Alzheimer's disease. Other work is directed at examining its etiology to determine if there is a genetic or environmental component to the disorder. Another approach is the search for viral involvement in the disease. Scientists supported by NINCDS extramural research funds have done some of the most exciting work in this area.

The classical neuropathology of Alzheimer's disease is characterized by abnormalities of the cerebral cortex. The three pathological hallmarks of the disease are: neuritic plaques consisting of abnormal neurites associated in time with extracellular amyloid; intracellular neurofibrillary tangles consisting of accumulations of paired helical filaments; and granulovacuolar degeneration.

Recent studies by NINCDS grantees at Hopkins strongly suggest that the neurons in the nucleus basalis of Meynert selectively degenerate in Alzheimer's disease. The cholinergic system is of particular importance, because of evidence implicating it in normal memory and cognition. Experimentally induced lesions in these areas have been shown to have profound behavioral effect in the rat. On the basis of these observations, it has been hypothesized that a selective lesion in the nucleus basalis is, in substantial part, responsible for the cholinergic abnormalities in the cortex.

A number of recent studies have pointed to a cholinergic deficit as a consistent feature of AD. Centrally active drugs that block muscarinic receptors have long been known to impair higher cognitive functions. Several groups have undertaken neurochemical analysis of the brains of AD patients who have died. In research aimed at characterizing the biochemical alterations in AD, it was found that the acetylcholine muscarinic receptors of the cortex are maintained even though there may be a 75% to 95% loss of cortical choline acetyltransferase. Localization of this synthetic enzyme and its receptor is being pursued in human and animal brain tissue by enzyme immunohistochemistry and radiography.

A detailed analysis of the basal forebrain-cortex connections of the rat revealed that excitotoxin lesions, affecting the diagonal band and medial septum, decrease choline acetyltransferase activity up to 40% in the occipital cortex and by 64% in the hippocampus. These results indicate that neurons originating in the basal forebrain complex are the predominant source of cortical cholinergic innervation. Nucleus basalis projection to the cerebral cortex was shown to regulate muscarinic acetylcholine receptors. These studies continue to be consistent with the hypothesis that acetylcholine decrease is a cause of at least part of the memory loss in Alzheimer's disease.

In bovine spinal cord, isolation of intact neurofilament results in enrichment of the triplet polypeptides which constitute about 90% of the total isolated intermediate filament protein. A new protein has been isolated and will be studied for its possible relation to the paired helical filaments of Alzheimer's disease. Evidence from other laboratories using cathepsin-D to degrade neurofilament protein also indicates that abundant cross-reactive polypeptides occur in neurons and are related to the normal metabolism of neurofilaments. Studies also 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 cell body.

Researchers are immunochemically isolating and characterizing the Alzheimer neurofibrillary tangles and the cross-reacting antigens from normal young human and animal brains. Absorption experiments demonstrated that the cross-reacting antigens of the tangles are neither tubulin nor neurofilament triplet polypeptides. Immunocyto-chemical studies indicate that at least four different cross-reacting antigens or antigenic sites of the tangles are present in normal brains. The relationships of each cytostructural element to the others is being explored.

A large program project on "Senile Dementia: Alzheimer and Vascular Disorders" at Albert Einstein College of Medicine is devoted to an interdisciplinary approach to studying the dementias. Clinicians, biochemists, neuropathologists, neurophysiologists, psychologists, mathematicians and many others are investigating the origin of these diseases and developing appropriate treatments.

The program has three major sections. One section consists of laboratory studies relating to the etiology and pathogenesis of senile dementia, particularly of the Alzheimer type. A second section continues several clinical and psychological studies of Alzheimer's disease patients now in progress. The third section consists of a large prospective study of about 400 people, aged 74-85, drawn from two nursing home facilities and "normal" elderly volunteers drawn from the community.

A large number of patients were investigated prior to death by detailed clinical and psychometric testing, and after death and autopsy by detailed neuropathologic and morphometric techniques. Concentrations of somatostatin and substance P were reduced in some of the patients and age-matched controls. At least half of the patients have only neuritic plaques in the cerebral cortex while the others have both plaques and tangles. In cell counting studies it was found that the concentration of plaques correlates with the loss of large neurons only in the superior temporal region. Nevertheless, the number of plaques continues to correlate well with the mental status score.

An extensive examination of the 400 subjects has been carried out. Preliminary data suggests that in a population of elderly, asymptomatic individuals there is a high incidence of arrhythmia manifested by frequent ventricular ectopic beats and bradycardia. Studies using oral choline chloride and oral physostigmine with supplemental lecithin have not demonstrated a dramatic improvement or reversal of the disease process. The studies with physostigmine are continuing.

CONTRACT NARRATIVE
Demyelinating, Atrophic and Dementing Disorders Program, NINCDS
October 1, 1982 - September 30, 1983

INDIANA UNIVERSITY, INDIANAPOLIS, INDIANA (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: $152,521

Objectives: This contract will continue the work of the National Research Roster of patients with Huntington's disease (HD) and their families for an additional three years. The Roster is serving two functions in stimulating and supporting research on Huntington's disease: 1) provide statistical and demographic data on a large sample of individuals and 2) serve as a link between investigators and affected families.

Major Accomplishments: The HD Research Roster was established at Indiana University in September, 1979. The 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 from 47 states have been entered. The Roster has received over 800 completed questionnaires from affected individuals. Families from Canada, Greece, and Venezuela add more than an additional 2,000 people to the Roster data base.

The major use of the Roster to date has been for descriptive statistics. The existence of a putative maternal protective factor on the age of onset of the clinical manifestations is strongly supported by Roster data. This new information has pointed up the need for additional research projects, especially the analysis and sequencing of mitochondrial DNA. Requests for information have been received from investigators wishing to contact families with Huntington's disease of a specific type or living in a particular locale. The Roster Contractor has served as an intermediary, providing investigators with the most suitable families possible. Confidentiality is strictly maintained unless written permission is granted by the individuals concerned. The first publication using Roster data is in press.

Proposed Course of the Contractor: The Contractor for the Roster is expeditiously carrying out the goals described in the work scope and proposes to continue this work until the termination date of this contract on November 30, 1983.

DEMYELINATING AND SCLEROSING DISORDERS

The Demyelinating and Sclerosing Disorders grant portfolio includes research relevant to multiple sclerosis (MS), amyotrophic lateral sclerosis (ALS), and the ataxias. As of July, 1983, there are 94 active grants, including nine research centers. Total funding of this research is approximately $13 million.

Multiple Sclerosis

As of June 1983, there are 38 active grants in the multiple sclerosis subprogram, including five MS and two ALS-MS research centers. Total funding in support of these activities is approximately $8.2 million.

Epidemiologic studies indicate geographical areas of high and low prevalence for MS. Studies of migrant populations strongly suggest that MS is acquired in childhood although the clinical disease is not usually manifested until adult life. The disease may be initiated by environmental agents, probably viruses. In addition, current data indicate that susceptibility to the development of MS is determined, in part, by genetic factors. It is likely that the lymphocyte and macrophage abnormalities in MS are inherited.

There is no proven safe and effective treatment for MS. ACTH and steroids continue to be used to treat the exacerbations of MS. This Institute currently is supporting five randomized and controlled clinical trials of the following agents: 1) Azathioprine, and prednisone with azathioprine in chronic progressive MS; 2) Co-polymer I in exacerbating-remitting MS; 3) Co-Polymer I in chronic-progressive patients; 4) Plasmapheresis and cyclophosphamide in the treatment of exacerbating-remitting MS; and 5) Intrathecal interferon. Because these are double-blind studies, the interim results are not available.

Animal models of virus-induced and immunologically-induced demyelination are used to investigate the morphological and immunopathological features of myelin injury. One such excellent model is experimental autoimmune encephalomyelitis (EAE). Another model induced by Theiler's virus is characterized by viral persistence in the central nervous system tissue. Studies demonstrate that the demyelination in this model is probably immune-mediated.

A scientist at St. Lukes-Roosevelt Hospital Center in New York demonstrated prevention and/or suppression of EAE in 3 species of animals by immunization with EAE-inducing lymphocytes. Antibodies isolated from immunized animals prevented transfer of EAE to normal recipients. This research provides an interesting approach to arresting MS.

For years immunological research in MS patients and animal models was focused on cellular immunity. Renewed interest in humoral immunity now provides a balanced research thrust. Investigators at the Albert Einstein College of Medicine have shown that antibodies to myelin lipids are needed during immunologically-mediated demyelination, and that basic protein, traditionally the major antigenic component of myelin, plays an important nonspecific role. The demyelination is enhanced by the presence of T-cells which were stimulated by other proteins, and by an antibody to a lipid, such as galactocerebroside. This work underlines the

usually de-emphasized role of antibodies in autoimmune demyelination. This finding might help not only to understand demyelination in multiple sclerosis but also provide a new approach to manipulation of the immune system in therapeutic trials. Recently these investigators also demonstrated that in acute EAE, T-cells invade the white matter whereas the antibody-producing B-cells remain in a perivascular location.

Investigators at the University of Southern California School of Medicine are exploring basic mechanisms relevant to the viral hypothesis by studying a virus-induced disease in mice. When mice were infected with a JMH virus at an early age and maintained to adulthood, they developed paralysis and other neurological signs. Pathological examinations of the brains of these mice show demyelination similar to that seen in MS patients.

Multiple sclerosis was re-evaluated on the premise that viruses might be harbored in the tissues in a covert state. Because MS patients have an unusually strong immune response to measles virus, this microorganism has been a primary suspect. Using hybridization techniques, a scientist at The University of California in San Francisco discovered measles virus genes in the brain tissue of six patients with MS. Although early results were promising, subsequent studies of brains from non-MS patients have revealed no significant differences, thus excluding measles from active consideration at this time.

The axonal disease research group at Stanford Medical School and the Palo Alto VA Medical Center, is studying cellular mechanisms which mediate the growth of normal axons and the regeneration of injured axons. The response of axons to demyelination is also being examined. Morphological and pharmacological probes are used to examine the pattern of distribution of ionic channels in normal and diseased axons. In healthy myelinated fibers, the sodium channels necessary for impulse conduction are confined to the regions in which the myelin is normally absent. This group has shown that, following demyelination, the denuded axon membrane develops sodium channels. This membrane plasticity may be relevant to mechanisms of recovery from demyelination.

Amyotrophic Lateral Sclerosis

As of July 1983 the amyotrophic lateral sclerosis subprogram had 12 active grants which included two centers devoted to ALS and two dedicated to research on both MS and ALS. The total cost for these research activities is approximately $2 million.

The motor neuron disorders, e.g. amyotrophic lateral sclerosis, constitute a spectrum of neurological disorders characterized by weakness, muscle atrophy, and widespread denervation. 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. Some of the familial cases of ALS are inherited as an autosomal dominant. In many families the mode of inheritance is not well defined. Most of the cases of amyotrophic lateral sclerosis are sporadic.

At present, there is no effective treatment for ALS. Drugs can be used to relieve excessive salivation. Putative 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.

Investigators at the Johns Hopkins University have found two inherited forms of canine ALS in Brittany Spaniels. One type is rapidly progressive, and the other is slowly progressive. The rapidly progressive form is an expression of homozygous inheritance, and the slowly progressive is the result of the effect of a modifying gene. A defect in the cytoskeletal protein of motor neurons was found in both forms.

The semi-quantitative neurological evaluation of over 170 patients at the Saint Vincent's Hospital and Medical Center in New York has shown that the course of ALS may be defined by the rate of progression as rapid (14%), moderate (30%) or slow (56%). Electron microscopy of ALS brains and spinal cords reveal chromatolysis of motor nerve cells. Spheroid accumulations of neurofilaments, usually located in the proximal portion of the axon were recently found more peripherally in a few cases of rapidly progressive ALS.

Elevated levels of immune complexes were found in the blood, brain and spinal cord of ALS patients. Immunological examination of these complexes revealed that they contain antigens of the enteroviruses, coxsackie and polio. This may be a significant finding since increased cellular immunity to poliovirus in ALS has also been observed.

An abnormal ganglioside distribution was found in brain and spinal cord of ALS patients. This may imply a possible metabolic block in the biosynthetic ganglioside pathway. Gangliosides may act as receptors for growth factors. Since nerve cell culture studies suggest that gangliosides had growth-promoting activity, it would be important to establish their putative role as an intermediary for nerve growth factor.

Infectious Diseases of the Nervous System

In fiscal year 1982, 30 grants were active in the infectious diseases subprogram. This includes three centers. Total cost for these research activities is approximately $3.4 million.

It is suspected that many neurological disorders are caused by viruses. These include Reye's syndrome, Guillain-Barre syndrome, multiple sclerosis, amyotrophic lateral sclerosis, Creutzfeldt-Jakob disease, and some forms of Parkinson's disease. Therefore 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.

The spongiform encephalopathies include scrapie, transmissible mink encephalopathy, kuru, and Creutzfeldt-Jakob disease (CJD). The agents causing these diseases are transmissible but they have not yet been identified or characterized. At the University of California in San Francisco adaptation of strains of the CJD agent to guinea pigs and to mice has made it possible to perform biochemical and genetic analyses. Preliminary data suggest that murine genes may affect the incubation time of the CJD agent.

Elucidation of the molecular nature of the scrapie agent has been a formidable task because of its unconventional structure, the cumbersome animal assay system, and the lack of an in vitro system for its propagation. Recent results suggest that this agent, called "prion," consists of a protein and contains no nucleic acid, or the nucleic acid may be so small that it is not detectable by current methods. This exciting work requires confirmation.

Investigators at UCLA have been studying the persistence of canine distemper virus (CDV) in dogs with chronic neurological diseases. Brain cultures of dogs with old dog encephalitis and chronic distemper encephalitis yielded CDV without co-cultivation. Direct isolation of CDV from homogenized brain supernatant was not possible and only after cultivation in vitro did the brain material yield the virus. CDV isolates from dogs with chronic neurological diseases show a tendency to be more persistent in cell culture, and the mechanism of persistence was found to be different when compared to the laboratory strain of CDV. Persistence of the isolate was achieved immediately, whereas the laboratory strain needed seven passages.

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 "antigenic drift" which is the generation of viruses that differ from the original infecting virus. These virus variants could play an important role in the occurrence of the lesions and the clinical disease. Monocytes, found to be latently infected, are important in both occult and disease-producing phases of the infection. The search is underway for a macrophage-enhancing factor which may be induced by virus replication.

In some epidemics due to Togaviruses, neurological complications and fatalities are relatively frequent. Nevertheless, little is known about the immunological mechanisms which control infection of the nervous system and why a subgroup of an infected population develops neurological diseases. Sindbis virus, an alphavirus of the Togavirus group, is an excellent model for acute viral encephalitis. Recent studies have revealed the importance of the complement system, which modulates the Sindbis viremia prior to the generation of an antibody response in the control of virus invasion of the nervous system. In vitro studies show that purified Sindbis virus does activate the complement alternative pathway in the absence of antibody. Furthermore, an increased amount of virion sialic acid influences the degree of alternative pathway activation.

During persistence, viruses frequently occupy cells of the nervous and lymphoid systems. Such infected cells often show a disorder in their differentiated function. This leads to disruption in homeostasis. To understand better why virus might naturally persist in certain host cells, the replication of measles virus in several human lymphoblastoid cell lines and mouse hepatitis virus in oligodendrocytes is being studied. It has been found that during acute measles infection, two virus surface glycoproteins (hemagglutinin and fusion protein) appear on the surface of human cells resulting in a change of cell antigenic properties.

Ataxia

As of June 1983, the ataxia subprogram had 4 grants. The total cost for these grants is approximately $313,000.

The hereditary ataxias include a rather large number of diverse degenerative neurological disorders which are difficult to classify. Our knowledge of most of these disorders is still at the descriptive level and the current criteria used for the classification of ataxias are based mainly on clinical and pathological data. Progress has been made recently in the biochemical characterization of some of these diseases which could eventuate in biochemical criteria for their classification.

Ataxia is incoordination of movement which results primarily from dysfunction of the cerebellum and/or basal ganglia and their connections. Many conditions characterized pathologically by atrophy of the cerebellum and spinal cord, spinocerebellar degenerations, are hereditary ataxias. Friedreich's ataxia is a recessively inherited spinocerebellar degeneration that usually starts in the first or second decade of life. The disease is progressively disabling and the patient may become wheelchair bound several years later. Ataxia can occur as a disabling symptom in many other neurological disorders and is common in multiple sclerosis. Since it is a neurological symptom that has been relatively intractable to therapeutic manipulation, elucidation of the mechanisms underlying ataxia, and its successful treatment, would benefit a large number of patients with diverse clinical entities.

The basic biochemical defects in the majority of the inherited ataxias remain unknown. Since these afflictions are genetic, they are thought to result from mutations resulting in abnormalities of enzymes or structural proteins. A subgroup of patients with Friedreich's ataxia was found to have a defect in pyruvate metabolism. Recent studies suggest that these patients may lack the enzyme that is responsible for the interconversion of pyruvate to malate.

Patients with a recessive form of olivopontocerebellar atrophy were found to have a deficiency of the enzyme glutamate dehydrogenase. This enzyme, present in high concentrations in the brain, plays a central role in the metabolism of glutamate. This suggests that glutamate may accumulate in excessive amounts in the brain of patients with the enzyme deficiency which could cause the nervous system to degenerate. On the other hand, patients with dominantly inherited olivopontocerebellar atrophy were found to have altered levels of aspartate, glutamate, and taurine in the cerebellum. Several patients with diffuse central nervous system degeneration, but with ataxia as a prominent neurological symptom, have been found to have a deficiency of the lysosomal enzymes, hexosaminidase or arylsulfatase.

A team of medical geneticists and neurologists at the University of Mississippi Medical Center have been studying several families with dominantly inherited spinocerebellar ataxia for the past 15 years. In one large kindred, more than 750 descendants of the original affected individual have now been traced. Since the disorder is dominantly inherited, each child of an affected parent has a 50-50 risk for acquiring a crippling and eventually lethal disorder.

Scientists at the UCLA Medical Center, in collaboration with the investigators at the University of Hawaii, are carrying out histocompatability studies and linkage analysis of the genetic locus in ataxia patients to determine if the abnormal gene can be localized near a known locus of the human chromosome. They found that this gene is present close to the HLA locus in human chromosome 6 in some members of the affected families. In other families with dominantly inherited

ataxia there is not expression of a gene on the sixth chromosome, thus providing evidence for heterogeneity. These studies are important for genetic counseling. Due to the late age of onset of the disease, most individuals at risk will have already had children prior to the development of the symptoms.

A rat model of olivopontocerebellar atrophy has been produced using a toxic agent called 3-acetylpyridine which can block the metabolism of nicotinamide. This agent can selectively destroy the same kind of nerve cells that degenerate in patients with this disease. The toxin causes behavioral changes in the rat similar to those found in patients with ataxia.

Scientists at Johns Hopkins University are studying an inherited disease, characterized by ataxia, in Gordon Setters. Purkinje cells gradually shrink and disappear. It is conceivable that an understanding of this degenerative process and the effect of cerebellar input on the survival of neurons will lead to the development of an effective treatment.

NEURAL ASPECTS OF LEARNING AND BEHAVIOR, PAIN, AND NEUROENDOCRINE STUDIES

As of May 1983, 258 projects were active at a total cost of $20 million.

Neural Aspects of Learning and Behavior

A major goal of the neurosciences is to understand how normal and intact nervous systems function. Lesion induction, i.e. damaging or removing some structure within the brain and examining consequent alterations in behavior, has been a useful technique to determine brain function. For example, anatomical sites believed to play a role in memory have been selectively damaged and the ability of an animal to retain or relearn previously well performed activities is assessed.

Research on the neurochemical basis of learning and memory has been one of the major concerns in the neurosciences. The theoretical implication of the functions of brain peptides in higher processes of the central nervous system is of considerable interest. The clinical implications of research on the neurochemistry of learning and memory are appreciated when it is realized that there is no adequate therapy for human memory derangements.

The use of genetic techniques is another experimental approach to the investigation of animal brain function. Studies are being conducted on genetic variations in the number of nerve cells of the hippocampus of house mice. This work so far has demonstrated that the mouse hippocampus has at least five parts, each of which is under separate genetic control. The production of genetically variant strains of mice will enable investigators to evaluate the behavioral consequences of a genetically-determined anatomical variation.

Biochemical techniques are also useful in examining the causes of certain behaviors. Vasopressin, a neurohypophyseal hormone, has been implicated in memory processes in both humans and rats. There is much evidence that vasopressin is involved in the memory processes for active and passive shock-avoidance tasks. Oxytocin, another neurohypophyseal hormone, has been shown to have effects opposite those of vasopressin on avoidance behavior in normal animals. Indeed, it has been suggested that oxytocin is an endogenous "amnesic peptide." Recent clinical observations have demonstrated that analogs of arginine vasopressin, a posterior pituitary peptide hormone, can have an effect in humans as well. Under the influence of this drug, normal subjects are reported to have improved performance of a serial recall test, and two patients receiving electroconvulsive shock therapy showed significant reversal of the retrograde amnesia that invariably accompanies this treatment. These experiments represent a controlled laboratory demonstration which supports earlier claims of cognitive improvement following systemic administration of arginine vasopressin or its analogs. These interesting clinical observations have made even more compelling the search for the mechanisms of action for the behavioral effects of this hormone.

Recent studies have provided evidence that a monkey with a damaged hippocampus or amygdala may prove to be a promising animal model of human amnesia. It has been demonstrated that learning based on skills and procedures is spared in human amnesia while learning based on facts or data is not. Monkeys can be trained to

perform tasks similar to those which may be lost in human amnesia. Lesions are then made selectively in the hippocampus, amygdala or elsewhere. This approach has the potential of obtaining direct comparative data on both animal and human brain-damaged subjects and thus for understanding the basis of amnesia in humans.

Pain and Other Somatosensory Systems

In this category there are at present 21 projects. Two-thirds of these are related to pain and include studies of the ascending and descending pathways, mechanisms of pain, analgesia, and the neuropharmacology of nociception.

Electrophysiological and behavioral data suggest that specific tracts descend from the medulla to the spinal cord which mediate pain inhibition and narcotic analgesia. While the involvement of the medullary neurons in pain has been examined over the past decade, it is only recently that they have been shown to contain specific peptide neurotransmitters. Further, the coexistence of a peptide and monamine in the same neurons has been demonstrated by anatomical and biochemical studies. Both electrophysiological and anatomical studies are continuing to define the role of these descending pathways in the control of pain.

The discovery of pathways from the medulla to the spinal cord that contain peptide and monamine transmitters and that modulate pain sensation have led to investigations on the role of neuropeptides in synaptic transmission between small diameter sensory afferents and nociceptive neurons in the dorsal horn of the spinal cord. Substance P, somatostatin and cholecystokinin have been located within small diameter sensory afferents that project to the dorsal horn. Several lines of evidence now suggest that substance P may be a transmitter released from the central terminals of some nociceptive afferents. Evidence has been obtained that the spinal analgesic actions of opiates and opioid peptides may result in part from inhibition of substance P release from sensory afferent terminals. The serotonergic neurons of the medulla which also project to the spinal cord have been implicated in the regulation of pain sensitivity. Activation of these neurons inhibits the transmission of nociceptive information in the dorsal horn of the spinal cord and results in analgesia. A detailed study of the pharmacology, anatomy and electrophysiology of these neuronal systems should provide important information about the mechanisms by which they regulate the transmission of nociceptive information.

Other investigators have shown that separate opioid and non-opioid analgesia pathways exist in the brain. These studies could lead to the development of methods of pain control that do not have the problems (e.g., tolerance, dependence) that commonly accompany activation of the opiate systems.

Some of the pain projects involve a psychophysical analysis of stress-induced analgesia. For example, it has been noted that when an animal is severely stressed, its response to pain is significantly reduced. Repeated exposures to stress result in a progressive decline of the analgesic response. Virtually every type of physical stress examined increases blood plasma levels of beta-endorphins (the body's natural opiates), as well as ACTH and corticosterone (hormones normally associated with stress). However, not all stressors produce analgesia. Some stressors induce an analgesic response that is sensitive to

opiate receptor blockade by naloxone, whereas others cause a non-naloxone sensitive analgesia.

Studies utilizing various animal models have shown that pain pathways of non-primate mammals are quite different from those of humans. Substantial functional differences correspond to the anatomical and physiological differences between primates and carnivores and rodents. For example, investigators have shown in primates that the interruption of the major pain pathway, the spinothalamic tract, produces results identical to those obtained with the surgical procedure in humans. A corresponding hypoalgesia is not obtained in rodents or cats. This project is of clinical relevance. Study of the mechanisms of analgesia and pain in primates may lead to more effective means of pain control in humans.

Although much of pain research has been concentrated on central mechanisms of pain sensation, the fact is that pain in the vast majority of cases arises from conditions outside the central nervous system. These include causalgia, reflex sympathetic dystrophy, neuromas, chronic degenerative disc disease, 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 for understanding mechanisms of cutaneous pain in normal and injured skin. They are now studying how pain signals are produced in injured nerves. In this way they hope to understand how and why neuromas, nerve crush, and nerve regeneration cause pain. An additional objective of this work is to understand why electrical stimulation has sometimes proven effective in relieving pain. This therapeutic intervention represents one of the most significant tangible advances in pain therapy of the past decade. The procedure works well in a small number of patients. Elucidation of the mechanism of action may lead to improvement and wider utilization of this technique.

Neuroendocrine Studies

Currently this program supports 87 projects related to steroid hormones, neuropeptides and interaction of these endocrine systems with monamine neurotransmitters. Most of these projects deal with the identification of hormone receptors and neurosecretion. Related phenomena such as synthesis, storage, release, transport, conversion, inactivation, regulation, and characterization of the neuroendocrine peptides in the brain, hypothalamus, and pituitary and other parts of the central nervous system are also under study. Some projects address neuroendocrine functions which are related to behavior, such as thirst, hunger, body weight regulation, circadian rhythms, stress, and temperature regulation.

During the past few years many separate peptide substances have been identified and found to be present in significant quantities in the brain. Most of the peptides 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 of their precise

cellular and subcellular localization as well as topographical distribution in the central nervous system is essential.

Almost without exception, the highest concentration of these substances is in the hypothalamus. Several of these peptides have been demonstrated to control activity of the anterior pituitary. Others act in regions of the brain related to sensory conduction, pain sensation or modulation, and behavioral responses.

The identification of peptides in the central nervous system has stimulated intense interest in uncovering their cellular receptors. Current studies are directed at determining whether such receptors exist, where they are located (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. It has been shown 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. Endorphins appear to bind to both types of receptors whereas the enkephalins bind only to mu receptors. Morphine binds predominantly to mu receptors, and it has been suggested that dymorphine, 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 light microscopy.

Brain cells are protected from the effects of circulating peptides by the blood-brain barrier (BBB). The available evidence indicates that 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 the endothelia of cerebral vessels. Peptide binding to the BBB may generate the production within endothelium of second messenger compounds that are released into the extracellular space. Thus, mechanisms may exist for the rapid modulation of brain cell function by circulating peptides, without necessitating that the peptide actually cross the blood-brain barrier.

Feeding Behavior

The central nervous system is known to play an important role in body weight regulation. Recent studies in animals have implicated several brain peptides in the regulation of feeding behavior. Cholecystokinin, thyrotropin releasing hormone, and insulin are reported to be satiety factors, decreasing food intake, whereas beta-endorphin has been implicated in increased food ingestion. The sites of action of these peptides in affecting feeding behavior has been presumed to be within the CNS. Suppression of feeding by cholecystokinin has also been reported to be mediated through a parenteral site.

Another line of investigation suggests that the central monamine system modifies body weight regulation. These studies are based upon an animal model, genetically obese mice, in which abnormalities have been uncovered in the catecholaminergic system. In the diabetic mouse, reduction of central norepinephrine levels results in decreased food intake and significantly less obesity of the animals. In the most widely studied models of abnormal weight regulation, rats with hypothalamic lesions, altered autonomic function is

apparent. Data 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.

In humans a relationship exists between obesity and certain diseases. The determination of the neuroanatomical pathways involved in the control of food intake and body weight regulation, and the demonstration of brain abnormalities in genetically obese animals may prove useful in therapeutic approaches to obesity.

Temperature Regulation

Temperature regulation represents a complex interplay of several factors. Derangement of the circadian temperature cycle may occur, for example, as a result of hypothalamic injury, because of an imbalance of neuropeptides in the brain affecting the thermoregulatory system, presence of pyrogens, or a calcium/sodium imbalance in the hypothalamus.

Most fevers have their origin in peripheral tissue, but it is only through the action of pyrogens on central temperature controls that characteristic increases in body temperature occur. Despite the importance of these central events which have a well recognized clinical significance, their precise nature is still unknown.

Hypothalamic lesions produce devastating effects in people. Many of these lesions are caused by tumors or cysts arising from tissue at the base of the brain, and can be successfully treated if detected in time. The classic signs of hypothalamic injury, necessary in suspecting the diagnosis, often occur long after an injury. In the course of these studies on fever mechanisms in patients and in 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. These investigations are providing much information which may have direct applicability to neuroscience and patient care.

Neural Transplantation

The recently demonstrated ability of transplanted neural tissue to functionally integrate into the brain of a host provides an extraordinary experimental tool for basic and clinical research. Although human brain tissue grafts to treat neurological and psychiatric disorders in humans are not feasible currently, some modest beginning has been made in animal models. For example, the Brattleboro strain of rats which suffer from a genetic disease, diabetes insipidus, lacks naturally occurring hormones or peptides (e.g.vasopressin), and exhibits memory deficits. It has been found that transplants of fetal brain tissue containing vasopressin-producing neurons can integrate with host's brain resulting in the amelioration of symptoms of diabetes insipidus and memory improvement.

Another example of transplanted neurons reversing a functional deficit comes from a rat model of Parkinson's disease. Rats with unilateral destruction of the dopaminergic input to the caudate nucleus, develop contralateral rotational behavior in response to apomorphine as a consequence of supersensitivity to

dopamine. It has been shown that grafts of fetal substantia nigra tissue containing dopamine neurons significantly reduces the lesion-induced motor abnormalities.

These examples indicate that there are enormous opportunities for the exploitation of tissue transplantation techniques which will have an impact on many fundamental investigations as well as for the treatment of a variety of disorders of the nervous system.

TAB 7 -- STROKE & TRAUMA PROGRAM -- STP

ANNUAL REPORT
October 1, 1982 - September 30, 1983

Stroke and Trauma Program
National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

OVERVIEW OF PROGRAM

The Stroke and Trauma Program (STP) is responsible for research on stroke; cerebrovascular disease; injury to the brain, spinal cord, and peripheral nervous system; regeneration in the nervous system; positron emission tomography; primary and metastatic brain tumors; chronic and acute pain; and related subjects. The distribution of funds within the STP during fiscal year 1982 was as follows.

Research Category	Percent Funds
Stroke and Cerebrovascular Disease	37.6
Injury to the Brain, Spinal Cord, and Peripheral Nervous System	17.6
Regeneration and Plasticity	18.2
Positron Emission Tomography	21.3
Neoplasms of the Central Nervous System	2.6
Other	2.7

During fiscal year 1982, 256 applications were assigned to the STP. (There were 227 applications in fiscal year 1981 and 198 in fiscal year 1980.) Of the 256 applications, 76 percent were approved by initial review groups with concurrence from the NANCDS Council. (The approval rate was 63 percent in fiscal year 1980 and 71 percent in fiscal year 1981.) Of all applications assigned to the STP, 30 percent were funded. (Funding rates for fiscal years 1980 and 1981 were 40 percent and 29 percent, respectively.) For the study sections and special review committees that serve the STP, the median priority score of approved applications during fiscal year 1982 was 218, which is essentially the same as it has been for the past three years. (Median scores in fiscal years 1980 and 1981 were 221 and 222, respectively.) Although there was a modest increase in approval, the funding rate has remained stable since the significant decline from fiscal year 1980.

The twelve Cerebrovascular Research Centers are a main strength of the STP's stroke-oriented research. Each center focuses on one or more areas related to etiological, clinical, diagnostic, therapeutic, and basic pathophysiological processes. The disease process is becoming more clearly defined temporally and pathophysiologically, but these efforts have not yet led to clearly defined therapeutic interventions. Significant advances have been made, however, toward prevention of stroke through identification of predisposing high-risk factors. Some of these factors are amenable to control measures that can prevent or delay cerebrovascular accidents in some, but by no means all, patients. Large numbers of patients suffer cerebrovascular incidents that require aggressive therapy.

The Comprehensive Stroke Centers have pooled their substantial base of data from three areas (4,125 patients from Oregon, New York, and North Carolina) and have completed cross-comparisons. The results are being prepared for publication, and the data base is being used for the analysis of intercenter variability, risk factors, diagnostic algorithms, survival characteristics, and outcome patterns.

The preliminary analysis of the results of the "Collaborative Study of Extracranial/Intracranial Anastomosis" indicates extraordinary comparability of the treatment groups, a patency rate (from required postoperative angiogram) of greater than 90 percent, a completely acceptable surgical complication rate, and followup achieved for all but one of the 1,430 patients. Ancillary analyses should be extremely valuable for the field of stroke, particularly in terms of the basic historical and medical data that can be obtained from the large cohort available and the ability to determine predictive factors for surgical selection, predisposing prognostic factors that might be used for outcome projection, and the generation of research hypotheses.

The "Cooperative Study of Intracranial Aneurysm and Acute Subarachnoid Hemorrhage" was established to evaluate the treatment of intracranial aneurysm, specifically the paradoxical suggestion that patients in poor condition after subarachnoid hemorrhage who are operated on early do not seem to do as well as those for whom surgery is delayed. Waiting for the patient's condition to improve, however, increases the probability of a fatal rebleed. Thus, the optimal patient characteristics, laboratory data, and time to operate for subarachnoid hemorrhage must be determined. The large amounts of data from this diverse population of 3,000 patients could provide the basis for a rational assessment of the situation.

The "Clinical Study of Brain Resuscitation" was established to address the prevention of severe brain damage that often results when cardiopulmonary resuscitation (CPR) after cardiac arrest is not completely successful. The hypothesis is that a large dose of thiopental given as soon as possible would prevent or ameliorate cerebral anoxic events. Preliminary analysis of the 259 patients entered indicates excellent comparability between the cohorts of prearrest characteristics, good toleration of the treatment, and no major adverse sequelae. Complete analysis of the data has been started.

The major trial for evaluation of the efficacy of high-dose (relative to low-dose) corticosteroids in the treatment of spinal-injured patients has been completed. While the data indicate that high-dose corticosteroids do not alter outcome at six weeks, six months, or one year after spinal injury, the results demonstrate that carefully controlled clinical trials can be accomplished in the difficult field of spinal cord injury.

The improved survival rate for the severely brain-injured, as a direct result of the availability of the highly specialized intensive care units, has raised questions about predictive survival and the degree of disability to be expected. As a result of current studies, there is now more agreement about the types of diagnostic tests that provide the most accurate estimates of recovery. Noninvasive stimulation and recording of electrical activity from a variety of anatomical sites of the brain and spinal cord are proving exceptionally effective in predicting outcome during the period immediately after brain injury. These new techniques allow frequent monitoring for critical changes in brain function and thereby permit rapid adjustment of therapy in relation to such changes. A particularly important clinical finding is the observation that the extent of recovery from surgery to remove a blood clot within the cranium is in part dependent upon the time that is permitted to elapse between injury and surgery. Delay from injury to operation of less than four hours results in survival rates of as much as 70 percent, whereas surgery performed after four hours may meet with a survival rate as low as 10 percent.

Even though the recently acquired capability in intensive and supportive care has resulted in improved survival rates for individuals who sustain injury to the brain or spinal cord, the basic aspects of recovery remain to be understood. These cellular responses, or "secondary effects," in the injured nervous system include altered blood flow, swelling of tissues, and elevation of pressure with the brain. These reactions, in turn, may both attribute to and produce reduced oxygen, nutrient supply, and energy production, which results in a disturbance in cell metabolism and specific cellular functions. These resulting abnormalities may arise from the inappropriate activation of particular enzymes that break down normal constituents of the tissue and from the release of overly reactive molecules that interfere with normal cell functions and upset delicately balanced tissue-sustaining processes, including the control mechanisms responsible for blood vessel tone and blood clotting. Efforts to define these fundamental changes represent a relatively recent development in the field of injury.

In relation to the need to monitor pressure within the head after injury to the brain, there is now evidence to suggest that a normal computerized tomographic (CT) scan after injury is indicative of near-normal pressure within the brain. In studies of patients with severe head injuries and in coma, investigators are exploring the efficacy of barbiturates in reducing the disability that results from the injury.

In relation to the need to carefully define the two lesser-studied extremes of the problem of brain trauma, minor head injury, and coma, enough evidence has accumulated to suggest that even minor trauma to the brain can result in significantly altered behavior and cognitive function. Through neurological and psychological testing, the clinical consequences of minor head injury are being explored.

Injury to the spinal cord may be followed by a succession of secondary effects that appear to increase the possibility of disability and death. The responses to the nervous system to injury include swelling and diminished blood flow and (or) bleeding within the spinal cord, with the result that neuronal function is lost and muscles and limbs may be paralyzed. The STP supports research on the factors that lead to the secondary effects after nervous system injury with the expectation that more effective treatment of spinal cord injury would minimize or prevent disabilities such as paraplegia. Major goals in this area include determination of the secondary, "self-destructive" reactions of the cord to injury; development of sensitive diagnostic procedures for assessing the extent of spinal cord dysfunction; and adoption of appropriate therapeutic interventions to reduce the functional repercussions of spinal cord trauma.

The five Spinal Cord Injury Research Centers continue to contribute to clinical and fundamental research in the area of central nervous system trauma. Research teams in these Centers are exploring the physical forces that affect the vertebral column and its enclosed spinal cord; the effect of the initial injury on subsequent blood flow within the cord; the control of urinary bladder function after injury (paraplegics often die of kidney infections related to poor bladder control); and improved methods of diagnosis by electrical stimulation and recording from intact elements of the cord.

In the field of nerve regeneration, recent findings have revealed highly specific neurobiological properties between species and even within the same animal; generalization is no longer acceptable. Thus, equally specific biological and technical assays are being developed so that the effects of nervous tissues and

their environments on the regenerative phase can be accurately determined. In addition, a number of investigators are working on prosthetic devices that would facilitate or stimulate tissue repair. These activities extend from the development of simple polymers that may serve to guide regrowing nerve processes back to their original connections to the elaboration of sophisticated electronic and mechanical equipment necessary to activate potentially useful, but paralyzed, limbs and organ systems.

The major emphasis of the Stroke and Trauma Program will be to maintain an adequate base of excellent fundamental, applied, and clinical research. To that end, specific emphasis will be given to increasing the amount of stroke-related activity so as to bring the effort of the Institute more nearly in line with the importance of the disease process. Trauma remains an important area of research, with emphasis on the biochemical events and their clinical implications. Additional emphasis will be on increasing the number of training grants in the areas assigned to the STP as the beginning investigator provides new and original ideas.

CEREBROVASCULAR DISEASE

Pathophysiology of Stroke

For many years, the persistence of signs and symptons of ischemia for more than a few minutes signified to clinicians the presence of irreversible cellular damage to the brain. Recent experimental work, however, supports the concept that the brain is more resistant to ischemia than had previously been suspected and has raised the possibility of intervening successfully before damage becomes irreversible.

Attention is now being focused on a variety of factors that might contribute to irreversible cell damage. A complex picture is emerging of interacting and cascading events that tend to reinforce the initial insult and initiate biochemical reactions that ultimately destroy vital cellular elements.

It now seems clear that the severity of lactic acidosis during ischemia and hypoxia profoundly affects the cellular damage incurred. Results have also substantiated the suspicion that cell damage matures, or perhaps even develops, during the recirculation and reoxygenation period. Evidence is accumulating that one of the major factors leading to cell damage is a disturbed $C2^{++}$ homeostasis, secondary to release of Ca^{++} from intracellular sequestration sites and to influx of Ca^{++} from extracellular fluids.

Free-radical processes leading to peroxidation of unsaturated lipids have been hypothesized to initiate structural and functional damage in brain tissue during the ischemic or postischemic period. At the Eighth International Conference on Stroke and Cerebral Circulation in Feburary 1983, there was a report of direct evidence for lipid peroxidation induced by reversible global ischemia in rat brain. Lipid-conjugated dienes result directly from free radical-induced chain peroxidation. The investigators quantified conjugated dienes (CD) by UV absorption in total lipid extracts from brains of rats subjected to reversible ischemia.

Their results indicate that CD are potentiated by ischemia and are overtly generated by recirculation of compromised tissue zones; however, the function of oxygen radicals in the ischemic process remains an extremely controversial area. Another report at the "Stroke Conference" described a study of the kinetics of serum

prostacyclin (PGI_2) breakdown in 11 patients with thrombotic stroke. Serum PGI_2 degradation was evaluated by incubating standard PGI_2 with serum at 37°C and measuring the PGI_2 activity remaining at various time intervals. The preliminary findings indicate that PGI_2 degradation is accelerated in acute stroke. Since PGI_2 availability represents an important defense mechanism against thrombus formation, this defect may have important pathophysiological implications. Work is in progress to characterize the defect.

Stroke Therapy

Many areas of investigation leading to therapeutic intervention to reduce ischemic brain infarction are being actively pursued. The recent discoveries in the field of prostaglandins have added substantially to our knowledge of platelet and vessel wall interactions and have opened up exciting new therapeutic possibilities. Small numbers of patients who have not experienced irreversible brain damage are currently being treated with prostacyclin, a potent vasodilator and platelet antiaggregant. Experimental studies in animals indicate that calcium-channel blockers may improve the microcirculation and be particularly effective in conditions where there is a chance of vasospasm developing, as in subarachnoid hemorrhage.

Although numerous clinical studies and case reports of interventional therapy for cerebrovascular disease offer reasons for optimism, increased research efforts are needed to determine the efficacy of new treatments. The results have been controversial either because the available data could not withstand critical analysis or there has been a failure to maintain acceptable methodological standards such as proper controls. Frequently, insufficient information is available to bridge the gap between the first reports of efficacy and the design of a large, controlled, therapeutic trial. To meet this need, the Stroke and Trauma Program has negotiated Master Agreements with fifteen institutions that have the experienced personnel, patient population, and resources needed to perform specific, usually short-term, task orders related to the efficacy of new or untested treatment and management modalities for patients with specific cerebrovascular disorders.

The first Task Order is for a late Phase I and Phase II study of Naloxone in the treatment of acute cerebral infarction. The main purpose of the study is to determine the maximally tolerated dose of Naloxone in patients with acute cerebral infarction and to provide an estimate of the efficacy of Naloxone by the holders of Master Agreements qualified to conduct such studies in acute cerebral infarction. These studies should provide sufficient information to allow future investigators to develop a controlled, prospective, and randomized clinical trial for the treatment of stroke with Naloxone, should it be indicated by the results of this Task Order. A second task order is based on preliminary, but equivocal, evidence that reducing blood viscosity may be beneficial, if administered soon after the ictus in stroke-in-evalution. This second task order will therefore address the efficacy of hypervolemic hemodilution in the treatment of acute stroke.

SPINAL CORD INJURY

As a result of accidents, war, violence-related injuries, and a variety of disorders, a large number of young adults, young men in particular, have been relegated to limited and dependent futures as paraplegics. Estimates are that

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 does not immediately follow 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. When the factors leading to these secondary effects are better understood, more effective treatment of spinal cord injury should result and disabilities such as paraplegia could be kept to a minimum or reversed. Thus, research on spinal cord injury is being directed at several major questions, including explanations for the secondary, and presumably reversible, "self-destructive" reactions of the injured spinal cord to mechanical injury; development of sensitive diagnostic procedures to assess the extent of spinal cord dysfunction, as well as retained function; and appropriate therapeutic interventions to minimize the structural and functional sequelae of spinal cord trauma.

Research efforts directed at resolving the enigma of spinal cord injury and recovery continues to be dominated by the investigative teams located at Yale University, the Medical University of South Carolina, New York University, the University of Texas, San Antonio, and Ohio State University. Some shift in emphasis between clinical and basic research at these five centers has occurred recently. While the programs at Ohio State University and the University of Texas, San Antonio, continue to focus on very fundamental aspects of spinal cord function and pathophysiology, the other multi-project, multidisciplinary teams have added significantly to their clinical components while sustaining their basic studies.

The recent implementation of computerized data acquisition, storage, and analysis, along with a variety of refined diagnostic approaches employing electrophysiological testing and other assays, has led to renewed efforts to further refine diagnosis, prognosis, and treatment. In the realm of treatment for acute injury to the spinal cord, studies are currently underway to test for toxicity and side effects of potential treatment agents and associated regimens. Naloxone, an opiate antagonist, reputed to have a beneficial effect on blood flow in the injured cord, as a result of studies in animals, is at an advanced stage of preclinical-trial assessment.

The results of another clinical trial, the use of steroids in the treatment of acute spinal injury, are just now being released. Although the one-year post-treatment follow-up is yet to be completed, the six-week and six-month studies indicate that high doses of steroid are no more efficacious than low doses of steroid in ameliorating the effects of injury to the spinal cord.

Efforts to more fully appreciate the consequences of trauma to the spinal cord continue to focus on how blood flows to the injured cord; the ionic environment of damaged and adjacent tissues; the contribution of usual and unusual metabolic processes to the injury process; and the liberation of phospholipid constituents, by-products such as arachidonic acid and prostaglandins, and free radicals into the neural parenchyma and its vasculature. With the growing awareness of the manifold deviant behavior of tissue arising from injury, investigators are now

proposing a variety of theoretical interventions that could lead to lessened tissue disruption. Thus, methods are being considered to minimize or reverse blood flow alterations and myelin degradation. Other approaches could include the quenching of free radicals and the neutralization of prostaglandins. Nevertheless, additional studies on basic tissue alterations are required before the fullest extent of rational therapy can be tested.

When tissue disruption after injury is very extensive, several strategies may be used to enable patients to function with lessened discomfort and greater independence. The Laboratory of Neural Control of the Intramural Research Program and the Neuroprostheses Section of the Fundamental Neurosciences Program of the NINCDS (summarized elsewhere in this annual report), in conjunction with a number of university and medical center laboratories, are very carefully defining voluntary motor control under normal circumstances and devising means of restoring movement when purposeful activation of muscles has been compromised by injury to the nervous system. The Stroke and Trauma Program is supporting related studies of spinal cord function and kinesiology in the CNS-injured animal in an effort to reduce such post-traumatic complications as bladder infections, hyper-reflexia, and muscle spasms. These studies also provide insight regarding intact circuitry and latent pattern-generators that may ultimately be recruited in the rehabilitation of the disabled. Results of research on regeneration, as described elsewhere in the Stroke and Trauma Program's report also suggest the possibility of greater control over injury sequelae and regeneration processes and a concomitant improvement in outcome for those sustaining injury to the spinal cord.

In addition to the five larger centers, individual investigators are providing basic information on relevant topics. There are currently ten investigator-initiated research projects in areas relevant to spinal cord injury.

HEAD INJURY

Innovative and intensive care after head injury has resulted in improved survival rates for those who experience brain trauma. The adoption and implementation of a research protocol within the stringent diagnostic and treatment regimens of a highly structured intensive care environment appear to positively influence the outcome for brain-trauma victims. The diversity of ongoing research permits characterization of the studies in a variety of ways. Nevertheless, the current, major investigative thrusts appear to be in the areas of diagnosis and monitoring, treatment in the acute phase, post-traumatic evaluation, and basic studies on the fundamental aspects of cellular, tissue, and brain responses to injury and post-injury treatment.

The formal program on head injury resides primarily in five large multiple-investigator program projects and five individual research project grants. The breadth of the research may be illustrated by a brief description of the studies at the several institutions and brief commentary on findings not as yet described in the most recent annual report. For example, within the head-injury research program at the Virginia Commonwealth University at Richmond, Virginia, investigators are continuing to gather data on the origin, diagnosis, and treatment of the severely head injured. A clinical assessment of the worth of treating the comatose with barbiturates is under way.

Attempts to establish criteria for the need and approach to monitoring intracranial pressure (ICP) have shown that monitoring ICP is essential if low-density or

high-density lesions are detected by computerized tomographic (CT) scans. Patients whose CT scans are normal should be monitored when two or more of the following are noted: age over 40, blood systolic pressure less than 90, and motor posturing.

Studies on cerebral blood flow after injury show that some patients are in a clearly ischemic range despite normal or even high cerebral perfusion pressure. Induced arterial hypertension or administration of a bolus of mannitol results in immediate improvement of clinical condition or evoked responses. Thus, a small proportion of patients may benefit from this treatment.

Cardiopulmonary function is receiving renewed scrutiny as a greater appreciation develops of the subtle and not-so-subtle interactions between the nervous system and the cardiopulmonary system after general injury, or CNS injury, or both. In addition, multimodality-evoked potentials continue to be studied for their prognostic capabilities and for their value as indicators for early therapeutic interventions during the course of changing physiologic conditions in the injured.

Laboratory studies have revealed that at least a part of the apnea associated with concussion is caused by the release of endogenous catecholamines. Indications are that alpha blockade may mitigate this respiratory effect.

Investigators are attempting to elucidate the subtle and transient neural and vascular perturbations that occur after brain injury. These perturbations include the alterations manifested by the organelles of the axons.

The mechanisms controlling cerebral blood flow are being further elucidated through studies of experimental animals. A recently disclosed "autoregulatory response" to changes in blood viscosity may help explain the transient effect of mannitol on cerebral blood flow.

A number of hypotheses have been advanced to explain behavior of the cerebral microcirculation after injury. Although there may be broad acceptance of some of the concepts, extensive work remains to delineate the precise mechanisms. For example, free radicals appear to cause vascular damage and sustained vasodilation, but there is uncertainty as to which radicals are the ultimate culprits. These and related questions are the objects of continuing investigation.

The arachidonic acid cascade after injury is the focus of much attention. Results of previous studies have shown that prostaglandin levels are elevated after fluid-percussion brain injury. Results of current studies indicate that acute hypertension alone or fluid-percussion without hypertension are inadequate stimuli to induce an increase in cortical prostaglandins. This finding implies that trauma and the ensuing acute hypertension are both necessary to elevate cortical prostaglandins. These studies also further emphasize the involvement of oxygen free radicals in the pathogenesis of the microvascular lesions produced by experimental traumatic brain injury. Along the same line of inquiry, free-radical scavengers, such as catalase and superoxide dismutase, reduce pial arteriolar abnormalities observed after fluid-percussion brain injury. The effect is the result of the ability of the scavengers to inactivate free radicals and not the action of the scavengers on arachidonic acid metabolism. Other experiments in this area suggest that neuroblastoma cells in culture are a suitable in vitro model for studying receptor-mediated changes in cellular arachidonic acid metabolism.

Research in the central nervous system trauma program at the University of Texas, Houston, has been along lines of inquiry similar to those of other programs, particularly the use of multimodality-evoked potentials in assessing outcome and treatment in response to CNS injury and the characteristics and mechanisms of the cardiopulmonary response to head trauma. Investigative areas that have received considerably less attention in general are the coagulopathies and the metabolic and nutritional status associated with injury to the central nervous system. The frequency, etiology, effect, and remediation of disseminated intravascular coagulation and deep-vein thromboses are important considerations in brain injury, as are the pulmonary and infectious complications that may interfere with the stabilization and recovery process.

Researchers in the head-injury program at the University of Texas Medical Branch, Galveston, have devoted considerable effort to refining diagnostic and monitoring techniques to more quickly respond to the immediate clinical status of the patient and to project the likelihood of recovery.

Recent studies have revealed that changes in depth of coma are manifested in the rate of habituation of cortical-evoked responses. Early signs of recovery of attention are reflected in the gradual emergence of the late positive component of the evoked response to rare, as opposed to frequent, tonal stimuli. These investigators have also found that the proportion of delta activity in the EEG correlates negatively with the process of recovery as indexed by specific component scores of the Glasgow Coma Scale.

In contrast to the often stated resiliency of language after focal hemispheric injury in children, the Texas group has found that children who have severe, diffuse brain injury have no better recovery than adults. In fact, the children's recovery may be worse.

These researchers have also been probing the amnesic aspects of head injury and are further delineating impairments in acquisition versus those of memory. The Galveston group is also pursuing a number of interesting leads on the fundamental properties of brain. They have evidence to suggest that there may be capillary exchange systems, such as glutamate transport, that are specific for brain endothelium, as opposed to capillaries elsewhere in the body.

The head-injury program at the University of Pennsylvania is characterized by an approach that combines the clinical and experimental head-injury programs with experimental ischemia studies. Here, the investigators are continuing their efforts to further understand the pathophysiology of head injury that leads to cerebral hyperemia, which is observed in about half the individuals who sustain acute head injury. In the effort to resolve the dilemma of cerebral swelling, this group is attempting to determine whether a major factor in early cerebral swelling is an increase in blood volume that ultimately produces edema. Using positron emission tomography (PET), CT scans, and other sophisticated approaches, researchers are studying the regional metabolic heterogeneity within the brain. Information of this kind should provide new insight into the functional properties of normal as well as injured brain.

Other studies of patients include assessments of frequently used therapy, such as barbiturates, hyperventilation, and mannitol, on cerebral blood flow and regional utilization of oxygen. In addition, high-resolution CT scans and PET methods are

being used to detect microfocal edema or hemorrhage and metabolic alterations after axonal damage, respectively.

The more basic studies of the University of Pennsylvania researchers are focussed on the development of additional representative models of head injury, such as diffuse axonal injury (DAI), that may result in traumatic coma. These investigators are also studying the behavior patterns, neuropathology, axonal transport, glucose metabolism, regional energy state, and blood and tissue fluid kinetics associated with DAI. In the experimental ischemia program, they are attempting to disclose the effect of post-ischemic blood flow changes on alterations in ATP recovery.

In the brain-edema program at the University of California, San Francisco, attempts are being made to clarify the factors that contribute to post-traumatic edema in the central nervous system and the strategies appropriate to its correction. Current findings indicate that arachidonic acid and other polyunsaturated fatty acids released from neural phospholipids as a result of injury have the ability to induce vasogenic and cellular brain edema. The observed increase in water and sodium content is accompanied by decreases in potassium content and Na^+,K^+-ATPase activity. The induction of brain edema by arachidonic acid appears to be dose dependent and maximal between 24 and 48 hours after injection. Dexamethasone is reportably effective in ameliorating the edema, whereas the cyclo-oxygenase inhibitor, indomethacin, is not. Results of other studies have suggested that oxygen-derived free radicals cause damage of endothelial cells of the blood brain barrier and brain injury characterized by edema and structural damage of neurons and glia. Observations on the endothelium of brain capillaries disclose an abundance of circumferentially-oriented subplasmalemmal smooth endoplasmic reticulum, evidently a feature not observed in non-neural capillary beds. This and previously noted traits limited to the endothelium of brain vessels suggest significantly different capabilities between neural and non-neural capillaries. Other active projects of the program are directed at determining the metabolic mechanisms contributing to the functions of the choroid plexus, membrane methylation in brain edema, and the efficacy, or even disadvantages, of some forms of acute therapy for brain injury.

In addition to the aforementioned program projects, a number of research grants are directed at cellular and tissue features associated with minor head injury; behavioral and pharmacologic features of lesions localized to specific functional areas of the brain; and correlations of anatomical, functional, and biochemical features associated with cerebral trauma. The information base on head injury is growing in many promising directions. While many of the findings emanate from the head-injury program, significant contributions are also forthcoming from other studies, such as those directed at cerebrovascular function and stroke, where topics such as brain damage from blood vessel occlusion or hemorrhage are equally germane to head injury.

CNS NEOPLASMS

Primary and secondary tumors of the central and peripheral nervous system, as well as research on the diagnosis, biology, metabolism, and treatment of brain tumors, represent major responsibilities of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS). Much of this research involves the use of the latest advances in technology. For example, noninvasive means of detecting brain tumors include positron emission tomography (PET), which analyzes tumor metabolism, and computer-assisted tomographic (CT) scanning, which delineates

the anatomical variation caused by a brain tumor. In the NINCDS PET program, investigators are evaluating the metabolic activity, permeability and blood flow in tumors and in normal brain tissue and attempting to determine variations. The higher-resolution positron scanner, which is a step closer to autoradiography in vivo, is being used to study intracerebral tumors.

In a different category of sophisticated technology, scientists are producing monoclonal antibodies with high specific activity. These antibodies distinguish, and thus permit differentiation, between tumor and normal brain tissue. Monoclonal antibodies can be used for the study of the early development of tumors and analysis of the biochemistry of the antigens that react with antibodies. For example, monoclonal antibodies that are specific for neuroblastoma cells permit clinical scientists to study this type of tumor in greater detail. In addition, the use of two types of monoclonal antibodies has permitted unequivocal identification of neuroblastoma cells in bone marrow of patients who have this disease.

As heterogeneity becomes a major concern in the events of neoplastic disease, researchers direct their efforts toward basic biochemical research, cell kinetics, mechanisms of drug sensitivity and resistance, the possibilities of biological modification, and the control mechanisms related to tumor growth. Other research supported by the NINCDS is directed toward developing diagnostic and serologic tests for quantifying and determining the severity and rate of progression of nervous-system disease secondary to cellular damage. Because radio-potentiating agents may increase the efficacy of irradiation in the treatment of tumors, these agents are being thoroughly studied. Additional studies include the use of ultrasonic brain imaging; quantitative CT scan analysis of water and tissue concentrations associated with hydrocephalus and intracranial pressure resulting from tumor; experimental models of intracerebral tumors; and the relation of blood-brain barrier pharmacodynamics to therapeutic agents.

In a variety of tumor-model systems, the behavior of prostaglandin E and interferon with and without stimulation showed an increase in metastasis in the stimulated group. The mechanism of action is being elucidated. Microwave-induced hypothermia as a method of increasing the sensitivity of a tumor to ionizing irradiation and drug is being evaluated in animal systems as well as in pilot studies in man. Bio-engineering principles are being defined, and controlled hypothermal therapy can be achieved. The thermal distribution within tumor and normal brain will be more specifically defined, and the necessary antenna and focusing systems are being developed. Future investigations will include an examination of the disruption of the blood-brain barrier secondary to heating.

Utilizing the avian sarcoma virus-induced brain tumor, measurements of blood flow, glucose utilization, permeability characteristics and transport systems have been evaluated by quantitative autoradiographic methods. The results of these studies will yield a better understanding of the methods by which drugs can be more effectively delivered to tumors within the central nervous system.

Progress has been made in determining the fine structure of a series of virus-induced experimental brain tumors, such as RG2, 9L, H-54, and AVM sarcoma. Experimental markers have been used to delineate 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 define more specifically the fine structure relationships.

Greater emphasis is being placed on determination of the capillary and endothelial defects that occur in experimental gliomas.

Basic research into nerve growth factors (NGF) pertaining to tumor growth and differentiation provides important information about regulatory mechanisms. Current investigation in this area includes examination of the sensitivity of NGF receptor sites and mechanisms that control the affinity of NGF binding and promoter substances to several different compounds. For specific cell lines that are sensitive, resistant, or unresponsive to NGF, the morphological and biochemical differences are being examined.

Sensitive, resistant, and unresponsive neuroblastoma lines have been identified. These neuroblastoma cell lines are being used to examine the interaction of NGF, growth rates, maturation, culture, and tumor-age relationships. Using the same cell lines, other researchers are examining the functions of methyltransferase and its subcellular distribution. Research into the regulation of growth and differentiation makes use of a tumor model that is highly reproducible, has constant growth rates, metastasizes, secretes markers (catecholamines), and is eventually lethal.

With the availability of recent technological advances, patients with neuroblastoma can now be studied in greater detail. Although significant problems related to the detection, diagnosis, intervention, and treatment of brain tumors remain as major challenges, the rapid emergence of new technology offers hope for the future resolution of these problems.

NEURAL REGENERATION AND PLASTICITY

Studies relevant to regeneration and plasticity in the nervous system continue in the promising directions established in recent years. Animal models continue to be evaluated in the effort to disclose factors responsible for facilitating and inhibiting neurite outgrowth and interneuronal connectivity after injury to the nervous system.

A number of investigators are trying to detect the "signal" that enables an axotomized neuron to direct its synthesizing capabilities toward the restoration of a more usual cell configuration and message-conveying mode. Increasing evidence suggests that axonal transport, retrograde as well as anterograde, serves to convey this important message. It is possible that alterations in the constituents of retrograde transport are responsible for the reorganization of the neuron's biosynthetic processes and that near restoration of the milieu of axon and axon-tips leads to a return to a more basal level of neuron metabolism.

The characteristics of the metabolism of the injured cell, including the production and transport of cytoskeletal components, is receiving increased scrutiny. A number of investigators have disclosed that the restoration of severed or compressed axons can be accelerated by conditioning factors before injuring the axon. Further efforts in this direction may lead to a means of controlling the rate of neurite outgrowth, a condition that may have important implications when considered in the context of the heterogeneity of neural tissues and the programming of neural recovery in the complex environment of cells and cell processes. The complexity of the influences controlling nerve cell development and regeneration remains apparent. Numerous factors have been isolated that condition the environment of injured neural tissues; that influence, in part, whether neurons degenerate

or are sustained; and that determine the kind and progress of the recovery processes. Many of these trophic substances would appear to be specific for particular families of neurons, such as the type of transmitter for which a neuron is responsible.

Major concerns include the altered status of the tissues after CNS injury, including the blood supply, the reactive cells responsible for tissue cleanup, the cellular and extracellular constituents that provide (or that do not provide) the trellis for bridging the site of injury, and the supporting cell-to-neuron interactions that may enable (or deny) restitution of form and function. The interface of injured neuron and reactive glia (astrocytes) is the focus of efforts to determine whether intramembranous and intermembranous molecular differences may account for the different potentials for regeneration manifested by the relatively refractory mammalian systems and the more plastic infra-mammalian systems. In addition, the bioelectric phenomena associated with injured neural and somatic tissues continues to be explored, particularly in relation to growing evidence that some ionic environments are more conducive than others to regeneration and recovery of function.

Transplantation of neural tissues is receiving increased attention by those interested in the remediation of neural deficits, as well as those interested in basic questions of neural development, differentiation, and growth. Several investigators have established protocols for sustaining grafts of the spinal cord within the central nervous system, and these studies are to be extended in efforts to integrate grafted elements of the spinal cord (and other donor sites) into the vicinity of injured spinal cord. Other researchers are studying transplants (or grafts) in other regions of the nervous system. Thus, transplantation studies have focussed on the attributes of hypothalamic, paraventricular, frontal cortex, and other donor sites, as well as the responses of the recipient tissues. Observations made in any one region should provide information for other locales.

New or refined experimental approaches, methods, and techniques continue to evolve as evidenced by the numerous productive studies completed and the array of new, imaginative, insightful, and detailed questions raised. Research on regeneration and plasticity remains promising, and existing contributions suggest a growing understanding of the capacity of the nervous system to reconstitute itself, both with and without intervention.

PAIN

Despite universal appreciation of its importance, there are still enormous gaps in our knowledge regarding basic mechanisms and treatment of pain. Scientists in the Seattle Pain Center are studying the neuropharmacology and neurophysiology of pain in primates using methods involving complex learning behaviors that are directly comparable with those used to study laboratory pain in humans. The effects of various pharmacologic interventions on brain-evoked potentials are recorded from animals chronically implanted with stimulating and recording electrodes and related to lever-press escape responses. Results of this study may provide information about agents that can be used to avoid the many clinical and social problems associated with the development of psychological dependence on narcotic analgesics. Other projects in this center are directed toward defining chronic pain in terms of psychological and sociological variables to determine if demographic, personality, or activity patterns can be used to predict the likelihood of acute pain leading to chronic disability.

Attempts to define the anatomy, biochemistry, and pharmacology of a pathway between the trigeminal ganglia and the pia-arachnoid indicate that ipsilaterally projecting perivascular neurons within the pia-arachnoid arise from the trigeminal nerve, primarily within the region of its ganglia composed of cells comprising the first division. Results also show that substance P, a vasodilating peptide previously associated with transmission of nociceptive stimuli, is a neurotransmitter contained in trigeminal neurons that project into the pia-arachnoid and that this neurotransmitter is released from pial neurons in response to the drug capsaicin. These results, coupled with the finding that immunoreactive substance P-containing fibers are present in the adventitia of pial vessels, which suggests that substance P-containing trigeminal neurons mediate the transmission of afferent information (perhaps) of a nociceptive kind from pial vessels to the central nervous system. If neurotransmitter peptides are released from perivascular afferent nerve endings upon depolarization, receptor blocking drugs might be useful in inhibiting substance P-induced changes in vessel wall, thus blocking the transmission of vascular pain within the trigeminal system.

The mechanism of activation of pain-sensory neurons (nociceptors) has been difficult to study in vivo because the nerve endings are small and generally inaccessible for intracellular microelectrode recording, and the cellular and fluid environment of these endings that can be altered by noxious stimuli is difficult to control. These difficulties are being circumvented by growing pain-sensory neurons in cultures where their neurites are directly accessible. Excitation of pain-sensory neurons by the application of algesics such as bradykinin and prostaglandin E_2 that are released by damaged tissue has been demonstrated. These studies are helping to define the similarities and differences of cellular properties of nociceptors that innervate different regions of the body and to determine how these cellular properties are involved in pathological conditions such as ischemia, trigeminal neuralgia, and pain from burns.

IMAGING

Positron Emission Tomography

A major problem facing investigators who use positron emission tomography (PET) is the timely and accurate analysis of the data being accumulated. Of concern is the fact that the PET image shows physiological processes and not the anatomical region. Often it is desirable to accurately locate a specific anatomic area of interest and observe the metabolic rate in that area. A major effort is therefore being made to develop strategies for incorporating x-ray CT scan data into the analysis of the PET scan data.

PET is being used to establish physiological criteria for patient selection for extracranial/intracranial (EC/IC) bypass surgery based on measurements of cerebral blood flow (CBF), cerebral blood volume (CBV), and oxygen metabolism (CMRO2). Results suggest that a focal increase of CBV and decrease of CBF and CMRO2 may identify areas of ischemic non-infarcted brain and that these changes are potentially reversible if perfusion pressure is restored. Thus, the measurement of these parameters by use of PET may be of value in patient selection for EC/IC bypass surgery.

Subarachnoid hemorrhage (SAH) from the rupture of an intracranial arterial aneurysm with or without vasospasm produces significant depression of cerebral blood flow (CBF) and cerebral oxygen utilization (CMRO2), even in patients in

good clinical condition without focal neurological deficits. PET is valuable in measuring these parameters in patients with SAH. The studies are providing new information on the relation between brain blood flow and metabolism in SAH and cerebral vasospasm, which should lead to better understanding of therapeutic measurements for these disorders.

The feasibility of multiple studies of one patient in a single day with a ^{11}C-labeled tracer has been demonstrated with ^{11}C-deoxyglucose. Although the synthesis is comprised of a number of steps, the experimental design has been sufficiently simplified so that it can be readly done at two-hour intervals. The ability to perform multiple serial studies on a daily basis is of considerable importance for determining normal variations in one subject as well as reducing biologic variability in comparing different subjects. It is expected that multiple studies with more complex ^{11}C-labeled compounds will form a significant part of human study protocols in the future.

The study of neurotransmitter receptors is a rapidly expanding area of investigation. Some brain disorders, including schizophrenia, Huntington's chorea, tardive dyskinesia, and Parkinson's disease are believed to involve changes in the dopaminergic neurotransmission system. Autoradiographic studies in animals have shown that tritiated neuroleptic drugs such as spiroperidol localize selectively in regions of the brain that have elevated concentrations of dopamine receptors. Compounds of this type, if labeled with an appropriate positron-emitting radionuclide, are proving useful for the localization and quantitation of dopamine receptors in humans by use of noninvasive imaging techniques. ^{11}C-Spiroperidol has been synthesized in relatively high yield. This compound offers the potential for serial PET studies of receptors at short intervals. Thus, an experimental subject can serve as his own control before the administration of drugs or other stimuli in studies designed to elucidate the contribution of specific receptor binding to the resultant effect of these experimental treatments. Serial studies may also be of particular importance in kinetic studies of neuroreceptor and neurotransmitter receptor binding in vivo.

Patients with liver disease and normal control subjects are being studied after receiving injections of ^{13}N-ammonia and ^{15}O-water to determine the important clinical problem of ammonia intoxication. Preliminary results indicate that the mechanism for the increased sensitivity to toxins observed in subjects who have chronic liver disease may be related to the ease with which toxins enter the brain.

Patterns of local cerebral glucose utilization were measured with PET by use of the labeled fluorodeoxyglucose method in patients with Huntington's disease (HD), subjects at risk for HD, and normal control subjects. These data were correlated with CT measures of cerebral atrophy, with age, and with duration and severity of symptons. The results indicate that in HD there is a characteristic decrease in glucose utilization in the caudate and putamen, and that this local hypometabolism appears early and precedes bulk tissue loss. In contrast to senile dementia, glucose utilization in most HD patients is normal throughout the rest of the brain, regardless of the severity of symptoms, and in spite of apparent shrinkage of brain tissue. Finally, results suggest the possibility that the caudate may be hypometabolic in some asymptomatic subjects who are potential carriers of the autosomal dominant gene of HD.

PET also has significant diagnostic potential for the detection and evaluation of neoplasias of the central nervous system. The focus of the PET research on these neoplasias is on the metabolic consequences, the effects of corticosteroids on blood-brain barrier, the mechanism of action of specific chemotherapeutic agents, and the heterogeneity of activity within brain tumors.

Special PET Conference

The STP organized a special conference on Research Issues in Positron Emission Tomography, which was held June 16 and 17, 1983, in Bethesda, Maryland. The purpose of the conference was to provide a forum for identifying problems that limit progress in PET research, for considering possible solutions, and for exploring future trends in applying PET to the study of neurological disorders. For these purposes, national and international experts in PET were brought together to consider what is new in PET research, where PET research is headed, what the problems are, and how the problems might be solved.

The conferees considered three main topics: technical aspects of isotope synthesis and imaging, definition of normal functions by PET, and evaluation of abnormal and diseased states. In the session on models and technology, the speakers discussed subjects such as metabolic and functional models for the brain, measurement of cerebral blood flow, positron-labeled compounds, high-resolution dynamic PET, and prospects for accuracy and precision. In the session on normal physiology, the subjects included regional cerebral blood flow and volume, measurement of cognition and perception, dopamine and opiate receptors, regional brain pH, and evaluation of the blood-brain barrier. The session on abnormal and diseased states was devoted to subjects such as the use of PET in measuring cerebral aging and in determining the existence or extent of such pathologic conditions as cerebral ischemia, extrapyramidal disorders, Huntington's disease and Parkinson's disease, tumors of the central nervous system, altered glucose metabolism, schizophrenia and affective disorders, senile dementia, seizure disorders, epilepsy, abnormal protein synthesis, Alzheimer's disease, and trauma.

Nuclear Magnetic Resonance

Proton Nuclear Magnetic Resonance (NMR) Tomographic Imaging is being applied to the study of cerebrovascular disease. Investigators are determining the sensitivity and specificity of NMR in detecting cerebrovascular disease and comparing the results with those recorded from CT. They are correlating the findings of NMR with cerebral biochemical alterations, particularly those involving water, lipids, and proteins in cerebral infarction. Major hypotheses being tested are 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 period of cerebral infarction results from a change of water content, the alterations in the later stages being from a change in the lipid or protein content.

CLINICAL TRIALS AND COOPERATIVE STUDIES

A prospective, randomized, multi-institutional clinical trial of cardiopulmonary cerebral resuscitation was initiated in 1979 to study the effects of thiopental administered soon after an episode of cardiac arrest. The accession of patients

has been completed; 266 patients have been studied in American and European institutions. The statistical analysis is expected to be completed within the next few months. Careful monitoring of risk and benefit, as well as balance of multiple variables that might influence neurological outcome, has been maintained.

The Extracranial/Intracranial Arterial Anastomosis Study was initiated six years ago with the objective of determining whether this surgical procedure would reduce by 50 percent, 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 was closed, at which time there was a total of 1,450 patients from more than 60 centers in North America, Europe, and Japan. The next three years will provide for necessary patient follow-up. The last year will be the year for final data accumulation, analysis, and publication.

The high patency rate of about 90 percent after the surgical procedure indicates the skill of the participating surgeons as well as the feasibility of the procedure. The considerable difficulties, especially coordination and follow-up, inherent in a multi-center study have been successfully met to a great extent by this diligent and sophisticated group. The NINCDS Monitoring Committee for this study continues to meet regularly; the Committee is completely satisfied with the conduct of the study.

August 1983 begins the fourth year of a cooperative study to determine the optimal timing of surgery for intracranial aneurysm after subarachnoid hemorrhage. Timing is the most important question facing clinicians involved in the management of these cases. As of May 1983, 3,429 cases were registered. The registration in North America has been projected for completion in July 1983. Comparison of admission characteristics of early and late surgical intervals demonstrates consideration comparability. Sufficient sample size and appropriate distribution of risk factors should be available for final statistical analysis.

The efficacy of corticosteroids in the treatment of acute spinal cord injury in humans remains equivocal despite their widespread use in patient management. In nine centers, investigators are collaborating in a double-blind, randomized trial of a high dose of methylprednisolone versus a standard dose (1 g versus 0.1 g daily for 10 days). Analysis of the results of this trial have been completed for the 6-week and 6-month follow-up periods and one-year follow-up is presently being completed.

The analyses of the effect(s) of steroids take into account a wide range of important co-variables such as severity of neurological injury, height and weight, time from accident to starting steroid treatment, and associated injuries. Morbidity and mortality resulting from steroid treatment are also studied. Neurological recovery is measured by standardized neurological examinations that include motor function, pinprick, and light-touch sensation. Analysis of the early follow-up data from the study provided no evidence for a beneficial effect of the 1 g methylprednisolone dose on neurological recovery when compared with the lower dose. If this observation is confirmed at the one year follow-up, it may provide information for the direction of future randomized clinical trials. While the outcome at the first two follow-up points indicates no difference between the two treatments, the study shows the ability to conduct controlled clinical trials in the extremely difficult area of spinal cord trauma.

CONTRACT NARRATIVE
Stroke and Trauma Program, NINCDS
October 1, 1982 -- September 30, 1983

Institutions:

1. UNIVERSITY OF ROCHESTER (NO1-NS-8-2385)

2. AMERICAN HEART ASSOCIATION, N.C. AFFILIATE, INC. (NO1-NS-8-2386)

3. UNIVERSITY OF OREGON HEALTH SCIENCES CENTER (NO1-NS-8-2387)

Title: Comprehensive Stroke Centers

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. $10,000
2. $24,900
3. $10,000

Objectives: The objectives of these Centers are to:

Conduct a program of applied clinical research in which fundamental advances are utilized in the development of specific approaches for the prevention, diagnosis and management of cerebrovascular disorders;

Develop integrated and coordinated community resources to evaluate the results of research on the prevention, diagnosis, and treatment of cerebrovascular disorders; and

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 fifth year as a cooperative effort is directed toward developing and evaluating treatment models for stroke patients in three geographically distinct areas: the northwest (Oregon), northeast (Monroe County, New York), 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 have been authenticated. Cross-center comparison tables of this data have been prepared and an analysis of survivorship across the three centers is in progress.

Papers being prepared for publication will cover a description of the program, an analysis of diagnosis and survival, statistics on discharge and long-term functional status, and risk factors for stroke.

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 to 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 that are somewhat independent while retaining programs that have a certain amount of overlap. During the fifth year, the analysis of patient data has been done in accordance with guidelines established jointly by the three Centers.

Contractor	Termination Date
University of Rochester	6/28/84
North Carolina Health Association, Inc. (now American Heart Association, North Carolina Affiliate, Inc.)	5/31/84
University of Oregon Health Sciences Center	6/14/84

The completion of this work and the publication of its results is expected during fiscal years 1983 and 1984.

CONTRACT NARRATIVE
Stroke and Trauma Program, NINCDS
October 1, 1982 -- September 30, 1983

Institutions:

UNIVERSITY OF IOWA, COLLEGE OF MEDICINE (NO1-NS-3-2326)
UNIVERSITY OF CALIFORNIA, SAN DIEGO (NO1-NS-3-2337)
BOWMAN GRAY SCHOOL OF MEDICINE (NO1-NS-3-2317)
UNIVERSITY OF PITTSBURGH, SCHOOL OF MEDICINE (NO1-NS-3-2332)
NEW YORK UNIVERSITY MEDICAL CENTER (NO1-NS-3-2329)
KANSAS UNIVERSITY MEDICAL CENTER (NO1-NS-3-2327)
BOSTON UNIVERSITY SCHOOL OF MEDICINE (NO1-NS-3-2320)
UNIVERSITY OF MARYLAND SCHOOL OF MEDICINE (NO1-NS-3-2328)
UNIVERSITY OF CINCINNATI MEDICAL CENTER (NO1-NS-3-2324)
UNIVERSITY OF SOUTH ALABAMA (NO1-NS-3-2334)
YALE UNIVERSITY SCHOOL OF MEDICINE (NO1-NS-3-2336)
UNIVERSITY OF PUERTO RICO (NO1-NS-3-2333)
EMORY UNIVERSITY (NO1-NS-3-2325)
UNIVERSITY OF TEXAS HEALTH SCIENCES CENTER, HOUSTON (NO1-NS-3-2335)
THE UNIVERSITY OF PENNSYLVANIA MEDICAL CENTER (NO1-NS-3-2330)

Title: Cerebrovascular Clinical Research Master Agreement

Objectives: The objective of this Master Agreement is to assemble a group of investigators who have demonstrated their ability to conduct one or more task orders related to the testing of the efficacy of new, controversial, or proposed treatment and management of patients with specific cerebrovascular disorders.

Significance to NINCDS Program and Biomedical Research: Information will be developed from task orders concerning the maximally tolerated dose, potential side effects, pharmacology, and clinical value of a particular treatment. These studies should provide sufficient information to allow future investigators to develop controlled, prospective, randomized clinical trials for the treatment of stroke.

Proposed Course:

In fiscal year 1983, two task orders will be awarded: one for a late Phase I and Phase II study of Naloxone in the treatment of acute cerebral infarction and the other for a Phase II study of hypervolemic-hemodilution in the treatment of acute cerebral ischemia. The STP anticipates the award of an additional one or two task orders in fiscal year 1984, and several in fiscal years 1985, 1986, and 1987.

CONTRACT NARRATIVE
Stroke and Trauma Program, NINCDS
October 1, 1982 -- September 30, 1983

Institution: MAYO CLINIC, ROCHESTER, MINNESOTA (N01-NS-3-2350)

Title: Bibliographic Service on Cerebrovascular Disease

Contractor's Project Director: Robert G. Siekert, M.D.

Current Level of Support: $51,731

Objective: To provide for distribution of abstracts of selected articles from the current literature that are of interest to individuals in the field of cerebrovascular physiology and disease. The abstracts will be published in Stroke, A Journal of Cerebral Circulation.

Significance to NINCDS Program and Biomedical Research:

Research reports on cerebrovascular disease appear in a wide variety of journals including those in the fields such as neurology, neurosurgery, general medicine, radiology, and computerized tomography. The provision of abstracts from widely diversified journals in one easily accessible place for those interested in cerebrovascular research is an extraordinarily valuable, as well as efficient, aid for staying abreast of the literature.

Proposed Course:

The abstract service will be supported for three years.

CONTRACT NARRATIVE
Stroke and Trauma Program, NINCDS
October 1, 1982 -- September 30, 1983

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: Comprehensive Central Nervous System Trauma Centers

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. $200,000
2. $200,000
3. $250,000

Objectives: The purpose of this program is 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, the specific objectives are to:

Develop coordinated community resources by means of which developments in CNS trauma research can be evaluated on a community basis;

Foster clinical research on improved diagnosis and treatment of patients with CNS trauma; and

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 about 400,000 new cases of head injury, severe enough to be hospitalized. About half of these cases were only 24 years old or younger. In view of the youth of those incapacitated, the impact on national health and productivity is evident. Because of this, the NINCDS has had a special interest in the problem of CNS trauma, and it 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 after the injury. Through its research programs on head injury and spinal cord injury, the NINCDS is obtaining information important to patient care. 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.

Proposed Course: At least two additional years of modest support will be needed to complete existing and already planned research projects. Irreversible functional deficits, including coma, cardiac arrest, and other medical problems leading to a compromised blood supply to the brain or its components, are not infrequent consequences of head injury. Barbiturates are reputed to suppress the sequelae of cerebral ischemia and hypoxia when given soon after injury. Suggestions have been made that, when given in appropriate amounts and at the proper time, the drugs appear to afford protection from focal infarction, permit resuscitation from global ischemic anoxia, and 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 is being initiated to study the efficacy of barbiturates in moderating the effects of severe head injury, specifically increased intracranial pressure. Physiological and clinical parameters 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.

The three teams have also developed an instrument for assessing the extent of minor head injury in their respective locales, as well as the effects of minor head injury on the future performance of the affected individuals. The latter consideration is of extremely compelling interest and need in view of the hundreds of thousands of mild head injuries each year.

CONTRACT NARRATIVE
Stroke and Trauma Program, NINCDS
October 1, 1982 -- September 30, 1983

Institution: 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: $76,150

Objectives: The investigations are assessing 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 these 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. This research will also permit the investigators to describe quantitatively the neurological and behavioral effects of the surgical procedure and whether they are transient or lasting.

Major Findings: After cingulotomy, patients with chronic pain rated the intensity of their clinical pain significantly lower than they had before operation, and they 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, which suggests 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 that 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 it is a diagnostic tool for the physician. The acute form is usually self-limiting in relation to the acuteness of the pathologic process. Chronic pain, however, may have no biological function, yet cause extreme hardship for the affected individual, the family, the community, and the workplace. The costs to the American public have been estimated to be as much as $50 billion annually. In this study, the investigators are analyzing the efficacy of a surgical method of last resort that is employed to alleviate otherwise intractable chronic pain.

CONTRACT NARRATIVE
Stroke and Trauma Program, NINCDS
October 1, 1982 -- September 30, 1983

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. $190,000
2. $156,700

Objectives: The purpose of this program, initiated September 29, 1982, is to develop an animal model of reproducible spinal cord injury and to use the model to test drugs and other means purported to minimize the consequences of injury to the spinal cord.

Major Findings: The two research groups have directed their initial efforts at the development and refinement of a model of open-cord injury. Working alone and collaboratively, they are developing their lesion model and finalizing the testing procedures to provide easily reproduced and well-characterized protocols of the type that can be readily implemented by others interested in the characteristics of the injured spinal cord and the worth of therapeutic interventions. A closed-cord injury model remains to be developed.

Significance to NINCDS Program and Biomedical Research: There are about 200,000 spinal-injured people in the United States, with about 10,000 more individuals sustaining these injuries each year. The physical, emotional, and financial drain is enormous, especially so in view of the youth of those incapacitated. "Novel" therapy to minimize the disability (paraplegia and quadriplegia) are proposed periodically. The NINCDS is seeking an appropriate animal model to permit well-controlled trials of proposed treatments for spinal cord injury.

Proposed Course: The two phases of study require validation of a reproducible model(s) of spinal cord injury and the use of the model(s) to test any treatment considered promising.

TAB 8 -- OFFICE OF THE DIRECTOR OF INTRAMURAL RESEARCH -- ODIR/IRP

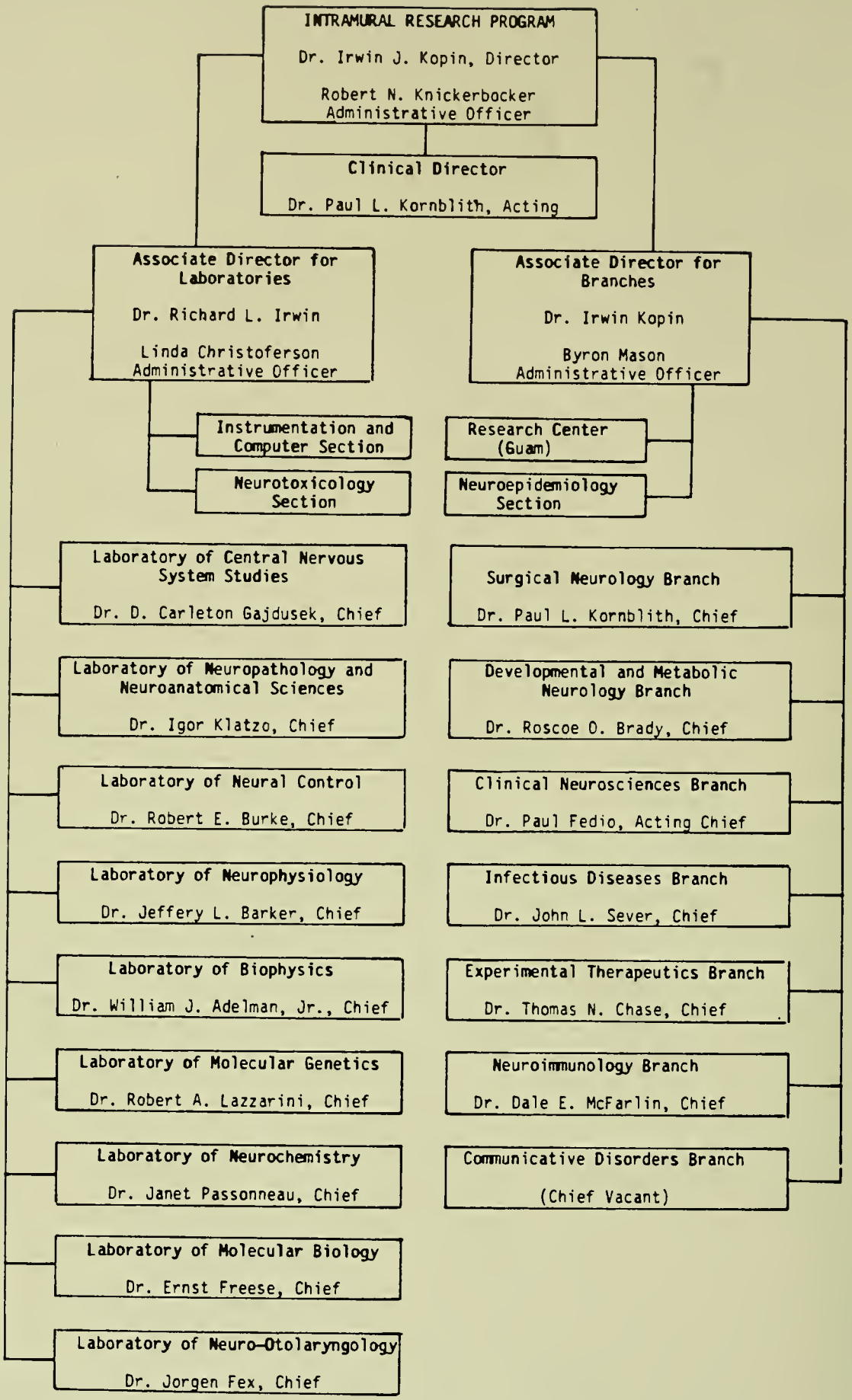
ANNUAL REPORT

October 1, 1982 through September 30, 1983

Office of the Director, Intramural Research Program

National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents


INTRAMURAL RESEARCH PROGRAM
Dr. Irwin J. Kopin, Director
Robert N. Knickerbocker
Administrative Officer
Clinical Director
Dr. Paul L. Kornblith, Acting
Associate Director for Laboratories
Dr. Richard L. Irwin
Linda Christoferson
Administrative Officer
Associate Director for Branches
Dr. Irwin Kopin
Byron Mason
Administrative Officer
Instrumentation and Computer Section
Neurotoxicology Section
Research Center (Guam)
Neuroepidemiology Section
Laboratory of Central Nervous System Studies
Dr. D. Carleton Gajdusek, Chief
Laboratory of Neuropathology and Neuroanatomical Sciences
Dr. Igor Klatzo, Chief
Laboratory of Neural Control
Dr. Robert E. Burke, Chief
Laboratory of Neurophysiology
Dr. Jeffery L. Barker, Chief
Laboratory of Biophysics
Dr. William J. Adelman, Jr., Chief
Laboratory of Molecular Genetics
Dr. Robert A. Lazzarini, Chief
Laboratory of Neurochemistry
Dr. Janet Passonneau, Chief
Laboratory of Molecular Biology
Dr. Ernst Freese, Chief
Laboratory of Neuro-Otolaryngology
Dr. Jorgen Fex, Chief
Surgical Neurology Branch
Dr. Paul L. Kornblith, Chief
Developmental and Metabolic Neurology Branch
Dr. Roscoe O. Brady, Chief
Clinical Neurosciences Branch
Dr. Paul Fedio, Acting Chief
Infectious Diseases Branch
Dr. John L. Sever, Chief
Experimental Therapeutics Branch
Dr. Thomas N. Chase, Chief
Neuroimmunology Branch
Dr. Dale E. McFarlin, Chief
Communicative Disorders Branch
(Chief Vacant)

Annual Report of the Scientific Director
of the
National Institute of Neurological and Communicative Disorders and Stroke
October 1, 1982 through September 30, 1983

The Intramural Research Program conducts most of its research efforts through direct operations of laboratories and clinics at the main NIH complex in Bethesda. A small portion of the research is performed away from Bethesda, at Fort Detrick in Frederick, Maryland, or at the Marine Biological Laboratory in Woods Hole, Massachusetts. In these facilities, Federal Government scientists and their support staffs continue to discover and produce new knowledge that aids our ability to prevent, ameliorate or cure neurological or communicative diseases. Ranging from chemical interactions of molecules to clinical trials of new drugs in patients, the studies contribute significantly to the explosive growth of new knowledge in the neurosciences and related diseases. The research projects are mainly scientist-initiated and all projects relate to the main mission of the Institute and NIH: the advancement of biomedical research for the ultimate alleviation of human suffering from disease or injury.

During the past year, the Intramural Program has found itself in a transitional managerial period. Stability has been maintained by the appointment of long-term staff members into key managerial positions while permanent staff positions were being filled. Funding, space use, personnel, and program level of effort have remained essentially constant during the past year. It seems of little consequence to restate the detailed information in the Scientific Directors' Summary of FY 82, since there have been only nominal changes. For this year's Scientific Directors' Summary, the Acting Director has chosen to summarize the major scientific findings of the Laboratories and Branches. Additional details about each study are included in the individual project reports.

The Neuroepidemiology Section's (ODIR) studies have for the first time shown that the risk of Alzheimer's disease is higher in one ethnic subgroup than another. It has also been found that the incidence and prevalence of stroke varies widely in geographic regions. These findings are considered of heuristic importance for future understanding and prevention of these neurologic disorders.

Scientists in the Neurotoxicology Section (ODIR) have developed new methods for studying the fusion of cell plasma membranes with transmitter storage vesicles. They have found that substantial structural rearrangements of membrane proteins and lipids are necessary for fusion to take place. They have isolated a soluble protein which enhances the ability of calcium to promote membrane aggregation.

Examples of major projects in the Instrumentation & Computer Section which have been either completed or appreciably advanced are: a redesigned patient activity monitor with fourfold memory capacity and twofold size reductions: a computer-based telecommunications interface that allows activity monitor data to be transmitted from anywhere in the country by telephone to central computer; a complete data acquisition and transmission system for monitoring physiological data from subjects in isolation rooms in the Clinical Center; a 32-channel state-of-the-art EEG amplifier system for topographic mapping of brain activity; an image processing system for analysis of ECAT images, autoradiographs, and 2-D gels; a new tissue culture voltage clamp system; a high-speed random access visual stimulus system for evoked responses; a multi-level four-arm rat maze with microprocessor control of stimulus presentation, data acquisition, and analysis.

In the past year the scientists of the Surgical Neurology Branch have gained new insights into three areas of the problems of human malignant gliomas. In the area of brain tumor chemotherapy it has been found that each of the three major drugs in use, BCNU, AZP, and cis-platinum, has a different secondary mode of action in addition to their primary alkylating effects. Using these different mechanisms and a microtiter assay, it is now possible to pre-select drugs for therapy of individual patients. In the area of brain tumor immunology, it has been found that the tumor antigens appear related to survival and that the expression of these antigens can be modulated by differentiating agents. Cellular immunology studies have shown that a membrane hyaluronic acid coating can impede lymphocyte-mediated destruction of tumor cells and that the tumor cells produce suppressor factors which also inhibit lymphocyte activity.

Studies of tumor metabolism have shown that there is a very high hexokinase enzyme level in malignant gliomas in culture. This high level of glycolytic activity has been found to correlate well with the observation that the uptake of 18FDG is significantly higher in the most malignant gliomas than in corresponding normal brain or in lower grade tumors. This difference in metabolic activity also has been shown to be useful in distinguishing between radiation necrosis and recurrent tumor.

A major accomplishment of the Developmental and Metabolic Neurology Branch was the development of an electroimmunoblotting procedure to differentiate between the neuronopathic and non-neuronopathic forms of Gaucher's disease. Discrimination between the two neuronopathic (infantile and juvenile) Gaucher phenotypes was subsequently obtained with a monoclonal antibody. These discoveries indicate that similar tests can be developed to distinguish clinical phenotypes in many genetic disorders.

After ten years of effort, the scientists of the Developmental and Metabolic Neurology Branch have succeeded in eliminating contaminating pyrogen(s) from placental ceramidetrihexosidase. This has allowed reinitiation of enzyme replacement trials in Fabry's disease.

The myelin-associated glycoprotein discovered earlier by the Developmental and Metabolic Neurology Branch has been shown to be the antigen in patients with peripheral neuropathy associated with IgM-paraproteinemias (plasma cell dyscrasias). Investigations with monoclonal antibodies indicate that natural killer lymphocytes share specific antigenic determinants with myelin associated glycoprotein (MAG) suggesting that the MAG or MAG-like molecule may play a role in cell-mediated immune phenomena.

Neuropsychological studies in the Clinical Neurosciences Branch of dementia, Huntington's and Alzheimer's variety, revealed distinct patterns of perceptual and memory impairment which correlate with pathophysiological changes. Intensive research with Alzheimer's patients has identified two distinct subgroups which share a salient memory and either a major visuospatial, constructional or language, communicative disorder. These correlate with hypometabolic regions (PETT) of the right and left temporo-parietal areas, respectively. Added studies of patients with temporal lobe epilepsy have identified distinct behavioral and intellectual problems along an ideative or emotional axis, corresponding to left or right brain insult.

The Infectious Diseases Branch developed three new tests for the rapid diagnosis of perinatal infections. An eight-minute test for antibody to rubella and a latex test of amniotic fluid for group B streptococcal infections now permits the rapid diagnosis of these infections. A new 4 1/2-hour test for herpes was also developed for use with human patients. An aerosolized measles vaccine was studied in field tests in Mexico and was shown to be effective in young children. The Branch also reported on several chronic infections. A model for Acquired Immune Deficiency Syndrome (AIDS) has been developed in monkeys and should be of value in the study of this human disease. These studies are also of importance in the control of the similar disease Simian Acquired Immune Deficiency Syndrome (SAIDS) in monkey colonies.

The human JC virus was shown to produce glioblastomas in owl and squirrel monkeys. The virus was also shown to be integrated in the DNA of the monkey cells. This suggests that the tumor arises from a single cell.

Persistent varicella infection was studied in culture to determine the mechanism of latency seen in zoster (shingles).

Oligoclonal IgG bands were found elevated in 95% of multiple sclerosis (MS) patients and a small number of patients with other diseases. This test is believed to be a useful test to aid in the diagnosis of MS.

Several major findings in the Experimental Therapeutics Branch contribute substantially to a further understanding of the involuntary movement disorders. Although substance P (a neural peptide) occurs in high concentrations in both substantia nigra and striatum, few substance P receptors occur in the former structure, indicating that substance P modulation of dopaminergic function takes place in the striatum. Cholecystokinin-octapeptide, a cotransmitter with dopamine in some basal ganglia neurons, has been found to be metabolized to fragments which in turn can effect the post-synaptic action of the parent neuropeptide. Application of the positron emission tomography/F-fluorodeoxyglucose (PET-FDG) method to the study of dementia produced data which indicates that Alzheimer's disease patients have preponderant dysfunction in the parieto-temporal association cortex. PET-FDG scans have also been found to localize epileptic foci in patients with partial seizures with exceptional accuracy, thus improving the success of surgical treatment.

The Neuroimmunology Branch has continued its fruitful studies on the mechanisms of demyelination and related disorders such as multiple sclerosis. An important finding was that transferred immune cells can directly produce the demyelinating disease process. Another important finding was that immunological changes occur in the spinal fluids of normal twins who later developed multiple sclerosis. This finding supports the concept that subclinical multiple sclerosis may be more common than previously recognized.

The Laboratory of Central Nervous Systems Studies continues research on viral diseases which occur world-wide. During the past year, the studies have created a wealth of new knowledge.

(1) The virus of hemorrhagic fever with renal syndrome was found to occur not only throughout East Asia, but also in city rats in the USA, and a new antigenically-related virus (Prospect Hill) was found in wild American field rodents.

(2) A long-term study of the slow virus disease, Kuru, has ruled out the presence of a non-human reservoir of the etiologic virus.

(3) A worldwide study of Creutzfeldt-Jakob disease has led to the finding that there is a stable rate of occurrence throughout the world with sporadic high incidence foci with a clear cut autosomal dominant inheritance. This implicates a single gene controlling suseptibility to the virus, a unique situation for a viral infection in humans.

(4) The laboratory scientists developed and promulgated improved procedures to prevent accidental transmission of Creutzfeld-Jakob disease in hospitals.

(5) In a search for the causative viral agent of Kuru, the Creutzfeld-Jakob disease, electron microscopic study of detergent extracts consistently revealed helical fibrils that may be the elusive physical particles of the etiologic pathogen.

Important new knowledge on brain edema and function of the blood brain barrier (BBB) have come from studies by the Laboratory of Neuropathology and Neuroanatomical Sciences. It has been found that even without brain tissue damage, the opening of BBB allows entry of serum proteins and increased water content--which can be experimentally prevented. They have also found that cerebrovascular smooth muscle cells have specific beta-2 receptors linked to adenylate cyclase. This implicates adrenergic innervation in the regulation of cerebral blood flow. The Section on Functional Neuroanatomy has made significant progress in the visualization of intricate membrane changes which control synaptic vesicle formation and exocytosis. The Section on Neurocytology has demonstrated that peripheral ganglia can be transplanted onto the brain surface and can influence central nervous system tissue. The Cellular Neuropathology Section has demonstrated that the Multiple Sclerosis strain of type 2 herpes virus can produce demyelination in optic nerves and spinal cord.

Culminating this year in the Laboratory of Neural Control is eight years of research effort on the behavior of muscle spindle afferents, motor neurons and muscles during normal motor behavior (locomotion). The neural organizations underlying coordinated movement in a limb are best described in terms of "task groups", which do not necessarily correspond to anatomically defined muscles. Certain muscles contain several task groups, while a given task group may encompass many muscles. In addition, the groupings change according to the task at hand, in relation to the kinematics of individual muscle activity. This framework provides a novel, and thus far very useful, conceptual basis for interpreting a very wide range of experimental observations on the control of movements. Studies on neural organization in the primate motor cortex provide strong evidence for the existence of much-debated "long-loop reflexes", by which proprioceptive input from muscle in the limb affect, by short-latency pathways, the firing pattern of output neurons from the cortex.

The Laboratory of Neurophysiology has perceived and seized upon some new opportunities for isolating specific populations of cells from mammalian central nervous systems. Methods of sorting the cells have been developed using newly available instrumentation which detects fluorescent probes. Application of the new methods and approaches are destined to significantly advance our knowledge of cell differentiation and function.

Nerve conduction and transmission both depend on ion conductances controlled by membranes. The Laboratory of Biophysics has demonstrated "instantaneous" sodium conductances changes in membranes and shown that the nerve impulse can be directly derived from the summation of single-channel unit conductances proving the continuity between microscopic and macroscopic conductances domains. They have also shown that the channel kinetics of the chemically activated cholinergic channel differ with various agonists. For the first time in neurobiology, the Biophysics Laboratory has shown that specific membrane current changes (of identified neurons) were causally related to associative learning of living animals. It was also possible to directly monitor the level of intracellular calcium as it regulates long-term modification of specific membrane currents during learning. It was further shown that a biochemical step, activation of a calcium and calmodulin-dependent protein kinase, mediates these calcium-induced changes of membrane channels.

1982 was highly successful for the Laboratory of Molecular Genetics. Each of the following three sections of the Laboratory made pivotal advances in their programs. In all cases the successes mark the end of the arduous developmental work and the beginning of the investigative phases.

Recombinant Genetics Section: The zenith of a year's research effort in the Laboratory of Molecular Genetics was the construction and positive identification of a cDNA clone of mouse myelin basic protein (MBP). This represents the first time a gene coding for a myelin constituent has been cloned. Indeed, it is the first time that a gene unique to the central nervous system has been cloned. The availability of this clone has opened wide vistas for research advances in this laboratory. Using this clone, the portion of the mouse chromosome that contains the MBP gene has been isolated and the flanking nucleotide sequences of the gene itself are being studied. Using the clone, it has been demonstrated that there are several species of MBP mRNA and that some of them are astonishingly large (2,300 - 4,300 bases). The amounts of these mRNAs present in mouse brain during the various stages of development has been quantitated, and it has been shown that 18 days after birth is the peak of MBP gene expression.

Of particular importance was the demonstration that the shiverer mutant mouse, which is deficient in its ability to myelinate CNS axons, lacks any detectable MBP mRNA. The fact that no mRNA was found, rather than an inoperative mRNA, suggests that the lesion lies in one of the regions of the mouse chromosome controlling the expression of this gene and does not lie within the gene itself.

Molecular Virology Section: VSV RNA polymerase is an enzyme complex consisting of a very large (L) and a small (NS) protein. This complex catalyzes the snythesis of RNA and its capping, ethylation and polyadenylation. The scientists have just succeeded in cloning and sequencing the entire NS and L genes--about 7,300 bases or 70% of the viral chromosome. From the nucleotide sequence has been deduced the amino acid sequence of the L protein. This detailed picture of the protein will allow the mapping of the active sites of this protein and an understanding of how the various activities of the protein are controlled.

Neural and Molecular Ultrastructure Section: The scientists have created and characterized panels of monoclonal antibodies and have developed new techniques for the electron microscope visualization of the assembly of the virus at the inside of the plasma membrane. Using these novel techniques, virus assembly has been inhibited by injecting monoclonal antibodies into living cells and thus establishing that a pool of unbound nucleocapsid protein exists in the infected cell. It has been possible with the new technique to visualize viral particles assembling at the cytoplasmic face of the membrane. Which viral proteins are present in the viral particles are now being identified. The understanding of how virus particles assemble will undoubtably lead to new knowledge about the processes of viral diseases.

Experiments in the Laboratory of Neurochemistry have shown that the immunosuppressive agent Cyclosporin-A prevents rejection of nerve allografts. In addition, Cyclosporin-A inhibited indefinitely rejection of nerve allografts in animals sensitized for rejection. In another study, the laboratory scientists have shown the existence in brain membranes of multiple forms of the ATPase sodium pump.

The Laboratory of Molecular Biology has continued studies on cell development and sporulation. The details of the many findings are best reviewed by referring to the individual projects appearing later. They have found that ribavirin, a drug used to treat herpes, affects cell division adversely and should not be administered during pregnancy. Receptor studies using human cells in culture have shown that certain nucleosides or butyrate induce the synthesis of beta-adrenergic receptors. When these compounds were used sequentially, three times more receptors were made than would be expected from an additive effect. Evidence has been obtained for the existence of cellular catecholamine transport sites with a unique, previously unrecognized specificity which is distinct from that of alpha- and beta-adrenergic transport and depends on a proton pump, which apparently is energized by ATP.

An important finding in the Laboratory of Neuro-otolaryngology is the demonstration that nerve cells in the efferent auditory system contain both enkephalin-like immunoactivity and acetylcholinesterase. These findings point toward a greatly expanded understanding of the neural function of the auditory system. New methods using brain stem slices have also been developed which permit a new approach to the study of nerve synapses in the cochlear nucleus.

ANNUAL REPORT

October 1, 1982 through September 30, 1983

Neuroepidemiology Section, ODIR
National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

Table of Contents (cont'd)

Annual Report
for Period October 1, 1982 through September 30, 1983
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 six 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; Lima, Peru; Mexico City, Mexico; and Quito, Ecuador. Additional courses will be held in Caracas, Venezuela; Nijmegen, the Netherlands; Bombay, India; and Jerusalem, Israel. A workshop on controlled clinical trials in neurology was held in conjunction with the American Academy of Neurology in 1982, and a course on the clinical evaluation of clusters of neurologic disease was held at the Academy meeting in 1983. Future symposia are planned in collaboration with the World Health Organization, the World Federation of Neurology, and the International Epidemiological Association. Neuroepidemiology has been selected as one of the four main themes for the next World Congress of Neurology in 1985. 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, Kenya, Nigeria, Mexico, Turkey, India, Spain, Italy, the People's Republic of China, and Peru, and have received inquiries from Ecuador, Tunisia, 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 clinical units in Italy to conduct case-control studies of clinically diagnosed cases of Alzheimer's disease. Similar arrangements are being made to work in conjunction with the Alzheimer's Disease and Related Disorders Association. 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. All identified cases of CP born to Rochester residents during a 27-year period were studied. The overall incidence rate of CP declined from 2.3 to 1.6 cases per 1,000 neonatal survivors. Correlation of birthweight-specific rates of neonatal mortality and CP incidence showed that for the low birthweight neonate, coincident with a marked drop in mortality, the CP incidence rate remained unchanged. For the newborn with birthweight over 2500 g., the rates of CP incidence and neonatal mortality declined in parallel. In a study of CP outcome, a decreased survival was limited to individuals who needed custodial or total nursing care. For the remainder of the case sample, all survived a minimum of 10 years, and in several of the cases there was resolution of the motor handicap.

Studies of neonatal mortality were initiated by the Section because antecedents of pre- and perinatally incurred neurologic handicap and those of neonatal death overlap. While uniform and complete case identification in a large population over a long period of time is not available for CP, infant death/birth certificate linkage provides such case identification for neonatal death. Using the infant death/birth file of the state of Minnesota, the Section is now completing two descriptive investigations of neonatal mortality: 1) delineation of neonatal mortality rates (NMR) by sex in gestational age/birthweight-specific subgroups for years 1970-1976, and 2) a study of sex- and birthweight-specific NMR trends for years 1967-1976. The future objective of both the Rochester CP incidence study and Minnesota NMR study is to conduct case-control studies in search of maternal, fetal, and obstetric risk factors of CP and of neonatal death.

The Section has conducted extensive investigations of primary intracranial neoplasms. First, problems with nomenclature and disease definition were resolved. A number of descriptive studies were carried out, revealing two patterns of age-specific incidence. Analyses of most population-based data worldwide demonstrated 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. A comprehensive study of U.S. and international mortality data for primary nervous system neoplasms over a 15-25 year period demonstrated an increasing death rate, especially among the elderly. This was thought to be due to improved diagnosis and case ascertainment. 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 (TIA) 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 do not 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 completed ischemic stroke incidence rates (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.

Previous studies of stroke incidence have generally utilized one of two techniques: a) survey of an entire community to identify all cases of stroke or b) survey of all community residents hospitalized for stroke in medical institutions serving that population. Rates derived from community surveys are usually higher than those obtained from hospital statistics. To quantify the size of the error inherent in using hospitalized cases, we applied both methodologies to the same population. Cases of completed stroke occurring among residents of Rochester, MN, during 1955-1969 were verified by neurologic review of data from a records-linkage resource. In this community, patients are hospitalized following stroke on the basis of

medical necessity. Records for all 993 patients were reviewed to determine whether the patient was admitted to an acute care hospital for the stroke. Overall, 69% of stroke cases were admitted to an acute-care facility. This study suggests that incidence rates derived from hospital data underestimate the frequency of new strokes by 25-30%; this discrepancy is most marked in the elderly. Another investigation based in this same community studied stroke in patients already hospitalized for other conditions. Sixty-five individuals suffered a first completed stroke while in a short-stay hospital for either a medical problem or surgical procedure. This represents 6.5% of all first strokes in the Rochester population. The percentage of all first completed strokes occurring during a short-stay hospitalization was slightly higher for women (8%) than for men (5%). In 74%, the stroke was directly related to medical conditions or surgical procedures. Etiologic factors preceding stroke, in order of frequency, were acute heart disease (21), major surgical procedures (10), fractures (8), leukemia or blood dyscrasias (5), acute gastrointestinal bleeding (3), and cerebral angiography (1). In the remaining 17 patients without an obvious event or clearly attributable etiologic factor leading to the stroke, all but 5 had either diabetes mellitus, chronic heart disease, or hypertension. There were 99 additional Rochester residents suffering a first completed stroke while in a nursing home or chronic care facility, raising the total strokes in residents of hospitals or nursing homes to 11.5% of all first strokes in the community.

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 two investigations. One is derived from a review of detailed clinical records utilizing a population-based, records-linkage system. 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 second investigation, a 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 have therefore utilized the resources available through the Israeli National Neurologic Disease Registry to identify all potential cases among the population of Israel. These cases were 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 pattern has emerged for those age 60 and under as has been described in previous studies for older individuals. The incidence rates increase with age, and the disease is slightly more common in women. Of particular interest is the finding that the risk of early-onset Alzheimer's disease (age 60 years and earlier) is significantly higher among Jews of European-American origin compared to those born in Africa or Asia.

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, the disorder 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, India, Chile, Tunisia, Senegal, and Venezuela), 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 Centers 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, 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, Alzheimer's disease, and multiple sclerosis); and 3) genetic and biochemical studies of hereditary nervous system tumors.

Collaborative studies are planned with personnel in LCS, DCBR, NIMH to explain our observations of altered dopamine beta hydroxylase and norepinephrine levels in blood and biopterin in cerebrospinal fluid (CSF) in genetic subsets of dystonia patients. Based on low CSF biopterin in a form of familial dystonia, biopterin was administered intravenously leading to brief improvement in several members of this family.

Genetic study of 41 monozygotic twin pairs and 19 dizygotic twin pairs, selected because at least one member had Parkinson's disease, revealed only one monozygotic twin pair and none of the dizygotic pairs definitely 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 from three of our studies 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 indicates life-long differences in personality are present in affected versus unaffected twins, as our preliminary study suggested.

The existence of a protective factor present in limited amount, supplied unequally to the twins in utero so that one twin is at less risk and the other at greater risk for Parkinson's disease, could explain these observations.

An hereditary leukoencephalopathy simulating MS, with onset at about age 35, is under study in a kindred with over 20 affected individuals. Derangement of the autonomic nervous system is often seen early in the course and when recognized, serves to distinguish this single gene disorder

clinically from multiple sclerosis of the chronic progressive type. Computerized tomographic scan changes are highly characteristic.

Our studies have led to the recognition of at least two distinct genetic forms of neurofibromatosis: 1) the classical form as described by von Recklinghausen, and 2) a form in which bilateral acoustic neuromas are the hallmark. We have focused on neurofibromatosis with bilateral acoustic neuroma. Efforts have been directed at improving and simplifying screening high-risk individuals, confirming diagnosis, and establishing criteria for intervention. Audiologic studies, including evaluation of auditory-evoked response and acoustic reflex decay, are a useful, non-invasive, means for early detection of acoustic neuroma and for following their growth.

In our first major study involving neurofibromatosis of the von Recklinghausen type, a multidisciplinary program is being prepared to evaluate specific neurologic and cognitive status in patients and their first-degree relatives.

Reviews are in preparation regarding the genetic epidemiology of movement disorders and of neurofibromatosis.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 01924-13 ODIR

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Clinical, Genetic, Pathophysiologic Study of Hereditary Movement Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Roswell Eldridge Medical Geneticist, NES, ODIR, NINCDS

COOPERATING UNITS *(if any)*
ET, IRP, NINCDS; HE, NHLBI; LCS, DCBR, NIMH; and Department of Neurology, University of Helsinki

LAB/BRANCH
Office of the Director, Intramural Research Program

SECTION
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 *(Use standard unreduced type. Do not exceed the space provided.)*

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, blepharospasm, 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.

Collaborative studies are planned with personnel in LCS, DCBR, NIMH 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. Biopterin administered intravenously has led to acute benefit in one form of generalized dystonia.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 01927-13 ODIR

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Clinical, Genetic, Pathophysiologic Study of Hereditary Nervous System Tumors

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Roswell Eldridge Medical Geneticist, NES, ODIR, NINCDS

COOPERATING UNITS *(if any)*
OP, 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
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 *(Use standard unreduced type. Do not exceed the space provided.)*

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; to evaluate present modes of treatment; and to develop methods for preclinical detection and screening.

Our studies have led to the recognition of at least two distinct genetic forms of neurofibromatosis: 1) the classical form as described by von Recklinghausen, and 2) a form in which bilateral acoustic neuromas are the hallmark. We have focused 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, are a useful means for early documentation of acoustic neuroma and for following their effects.

In our first major study involving neurofibromatosis of the von Recklinghausen type, a multidisciplinary program is being prepared to evaluate specific neurologic and cognitive status in a series of these patients and their first degree relatives.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02167-09 ODIR

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Genetic Epidemiology Studies in MS and Other Multifactorial Neurologic Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Roswell Eldridge Medical Geneticist, NES, ODIR, NINCDS

COOPERATING UNITS *(if any)* NI, IRP and OBFS, OD, NINCDS; Department of Neurology, University of Oregon; Department of Neurology, Rutgers University; Department of Medical Genetics, University of Indiana; Department of Neurology, Monmouth Medical Center; and Department of Medical Genetics, Howard 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:
2.5	0.5	2.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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.

Genetic study of 41 monozygotic twin pairs and 19 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 dizygotic group definitely 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 from three of our studies 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 indicates life-long differences in personality are present in affected versus unaffected twins, as our preliminary study suggested.

These observations are consistent with the existence of a protective factor, present in limited amount, supplied unequally to the twins in utero so that one twin is at less risk and the other at greater risk for Parkinson's disease.

An hereditary leukoencephalopathy simulating MS with onset at about age 35 is under study in a kindred with over 20 affected. Derangement of the autonomic nervous system is often seen early in the course and when recognized, serves to distinguish this single gene disorder from multiple sclerosis clinically. Computerized tomographic scan changes are dramatic.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02240-07 ODIR

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Epidemiology of Dementia

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Bruce S. Schoenberg Chief, NES, ODIR, NINCDS

COOPERATING UNITS *(if any)* Epidemiology, Demography, and Biometry, NIA; W. Massey, M.D., Duke Univ.; 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; L. Amaducci, Univ. of Florence; R. Katzman, Albert Einstein College of Medicine, New York

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 *(Use standard unreduced type. Do not exceed the space provided.)*

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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02241-07 ODIR

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Epidemiology of Cerebrovascular Disease in Adults

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

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:
2.8	2.8	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02243-07 ODIR

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Pediatric Neuroepidemiology

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
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., L.T. Kurland, M.D., Dr.P.H., and R.V. Groover, M.D., Dept. of Neurology, Mayo Clinic; L.L. Salkowicz, P. Gunderson, Ph.D., Minnesota Department of Health

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	3.5	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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.

The same Rochester, Minnesota records-linkage system was used to determine temporal trends in the incidence rates of cerebral palsy as well as the distribution of clinical subtypes and survival by clinical subtype, for the years 1950-1976. For the state of Minnesota, sex-specific neonatal mortality rates (NMR) in gestational age/birthweight risk subgroups were delineated for the years 1970-1976, and sex- and birthweight-specific NMR trends were determined for the years 1967-1976.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02297-07 ODIR

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Mortality from Neurologic Disorders: National and International Comparisons

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Bruce S. Schoenberg Chief, 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:
6.0	6.0	

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02299-07 ODIR

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Reviews of Epidemiologic Aspects of Neurologic Disease

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Bruce S. Schoenberg Chief, 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:
3.5	3.5	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02300-07 ODIR

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Clinical Course and Medical Care for Neurologic Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Bruce S. Schoenberg Chief, NES, ODIR, NINCDS

COOPERATING UNITS *(if any)*

J.P. Whisnant, M.D., Department 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:
2.2	2.2	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02301-07 ODIR

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Collaborative Studies of Less Common or Less Debilitating Neurologic Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Bruce S. Schoenberg Chief, 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; G. Roman, Bogota, Colombia; P.S. Spencer, Albert Einstein College of Medicine, New York

LAB/BRANCH
Office of the Director, Intramural Research Program

SECTION
Neuroepidemiology Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
4.5	3.5	1.0

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02305-07 ODIR

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
The Epidemiology of Intracranial Neoplasms

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Bruce S. Schoenberg Chief, 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:
2.0	2.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02307-07 ODIR

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Educational Resources in Neurological Epidemiology

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)

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:
3.0	3.0	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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 was held in Edinburgh, Scotland in 1981; a one-day symposium was held in Kyoto, Japan in 1981; a one-day course was held in the United States in 1982 and 1983; and one-day conferences were held in Ecuador and Peru in 1983. A textbook entitled Neurological Epidemiology: Principles and Clinical Applications was published during 1978, and a new international journal entitled Neuroepidemiology was begun in 1982.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02370-05 ODIR

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

*Racial and Geographic Differences in Occurrence of Neurologic Disease

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Bruce S. Schoenberg Chief, NES, ODIR, 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

Office of the Director, Intramural Research Program

SECTION

Neuroepidemiology Section

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
11.0	8.0	3.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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 Ecuador, Mexico, Nigeria, Peru, the People's Republic of China, Spain, and Venezuela. Pilot investigations have been successfully carried out in Ecuador, Mexico, Nigeria, Peru, and the People's Republic of China.

[Former title: Racial Differentials in the Prevalence of Major Neurologic Disorders and Surveys in Developing Countries.]

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02423-04 ODIR

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Development of Data Resources for Neuroepidemiology

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

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

Office of the Director, Intramural Research Program

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 *(Use standard unreduced type. Do not exceed the space provided.)*

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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02424-04 ODIR

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Standardized Nomenclature and Coding of Neurologic Diseases

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

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 *(Use standard unreduced type. Do not exceed the space provided.)*

To develop an internationally acceptable standard of nomenclature, classification, and coding of neurologic disorders.

TAB 8.B — GUAM RESEARCH CENTER, ODIR -- ODIR(GRC)

ANNUAL REPORT

October 1, 1982 through September 30, 1983

Guam Research Center, ODIR

National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

ANNUAL REPORT
October 1, 1982 through September 30, 1983

Guam Research Center
National Institute of Neurological and Communicative Disorders and Stroke

Kwang-Ming Chen, M.D.
Officer-In-Charge (Acting)

The Guam Research Center was established in June 1956 as the permanent field station under the Epidemiology Branch, NINDB, by Dr. L.T. Kurland. A qualified neurologist was recruited to be stationed on Guam to conduct epidemiological, genetic, clinical and neuropathological surveillance on the Chamorro population affected with a high incidence of amyotrophic lateral sclerosis (ALS) and Parkinsonism-dementia (PD). During the peak research activity of 1963-1965, there were four neurologists, one internist, one epidemiologist, one geneticist and a botanist/nutritionist physically stationed on Guam during this period.

The mission of the Center was to investigate the etiology of these diseases of the central nervous system by studying an isolated population with the highest reported incidence and prevalence of these disorders.

I. ACCOMPLISHMENTS

A. Epidemiology.

1. Steady decline in annual incidence and prevalence.

2. Rising age at onset of the disease with a nearly even male/female ratio.

3. Increased risk of developing ALS and PD among Chamorro long-term migrants to the U. S. mainland after exposure to the Guam environment.

B. Genetic Studies.

1. Low incidence among the offspring of doubly affected parent-pairs with ALS and/or PD.

2. No simple Mendelian pattern of inheritance was found.

3. Occurrence of ALS and PD among long-term Filipino migrants to Guam who share the same environment with Chamorros.

C. Clinical Studies.

1. Three patterns of progression of the clinical course.

2. Longer average clinical course (five years, 32% survival; ten years, 13% survival).

3. Stable five-year and ten-year survival rates over the past 20 years by grouping into five-year periods, indicating that the natural history of ALS has not changed for the past 20-30 years. On the other hand, PD showed a significant prolongation of the course since the usage of L-DOPA in PD patients.

4. Discovery of PD in 1961 with the clinical overlapping of PD and ALS suggesting a single entity with a spectrum of clinical expression and possibly a single etiology.

D. Neuropathology.

1. Neurofibrillary tangles (NFT) in Chamorro brains, 1960-1980:

	Number of Brains	% With Neurofibrillary Tangles
PD Cases	228	100
ALS Cases	200	99
Controls	280	70

E. Pathogenesis of PD.

1. Failure in both dopaminergic and cholinergic systems (nigrostriatal fibers and basal nucleus of Meynert).

F. Etiological Studies.

1. The nut of C. circinalis had been widely used as a staple food by the Guam Chamorros after the nuts had been repeatedly soaked, washed and later dried. The extract, cycasin, has been found to be highly toxic and carcinogenic, but its ingestion by laboratory animals did not produce neurologic deficits resembling motor neuron disease.

2. Unsuccessful transmission and isolation attempts for virus, both conventional or unconventional.

3. Evidence of increased intraneuronal deposits of aluminum and extraneuronal deposits of aluminum, calcium, phosphorus and iron in the anterior horn of the spinal cord and cerebral cortex (where neurofibrillary tangles predominantly occur).

II. FUTURE PROSPECTS

The natural history of ALS and PD with currently identified patients will be continued and is expected to be completed in another three to five years. The future projects depend on the development of new research proposals. The following projects could form the basis of future work:

A. to determine the incidence of ALS and PD among the Chamorros who were born after World War II.

B. To determine the incidence of ALS and PD among the second-generation Chamorros who were born on the U.S. mainland.

C. To test the hypothesis of the unitarian concept of a single disease entity of ALS/PD by:

   1. In-depth neuropathological study of mixed cases.

   2. Intraneuronal trace metal determination to prove beyond a doubt the excessive accumulation in both ALS and PD.

   3. Experimental production of neurofibrillary tangles and neuronal loss in laboratory animals by feeding low Ca and Mg, high Al and Mn in the diet.

D. Geophysical and geochemical studies on the mechanisms of transport of elemental trace metals (Al, Mn, P, Se, Fe, etc., which are high in the Guam soil) into the flora and fauna and then into humans.

E. Tissue culture of fibroblasts and neurons from ALS/PD patients to determine the possible existence of a defect in the DNA repair mechanism.

F. Neurochemical studies on choline acetyltransferase (CAT) and acetylcholine esterase (AChE) activities in PD brains to evaluate the central cholinergic system of the nucleus basilis (Meynert).

G. Chemical characterization of neurofibrillary tangles.

H. Prospective study of dementia using volunteers.

I. Experimental drug therapy of dementia, if promising therapeutic agents become available.

J. Determination of the incidence of ALS and PD among the offspring of doubly affected parents.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02570-01 ODIR

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Natural History of ALS-PD in Guam

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Bruce Schoenberg, M.D., Chief, Neuroepidemiology Section, ODIR, IRP, NINCDS

COOPERATING UNITS *(if any)*

NONE

LAB/BRANCH

SECTION

Guam Research Center, Office of the Director, IRP, NINCDS

INSTITUTE AND LOCATION

NINCDS, Tamuning, Guam 96911 & NINCDS, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
6.3	1.3	5.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

As a continuation of previous projects on clinical, pathological, and epidemiologic surveillance of Guamanian amyotrophic lateral sclerosis (ALS) and Parkinsonism-dementia (PD) in the Mariana Islands, a total of 112 cases, including suspects registered as of January 1, 1983, are to be followed at intervals of six months for detailed clinical descriptions of patterns of progression by a qualified neurologist until all of the patients expire. It has been learned that the average duration of ALS is 4.0 to 4.5 years after onset with a range of 2.0 to 25 years. The study of those long surviving cases (over ten years) has been completed. Clinically they showed three patterns: (1) onset with slowly but steady progression at the same pace throughout the course; (2) rapid progression to complete paralysis of the limbs within 1.5 to 3 years and then remaining practically stable for the next 5 to 10 years; (3) onset with minimal atrophy and weakness for the first five to six years and then rapid step-wise progression to death. A study of the neuropathology of these long-surviving cases by a guest neuropathologist from Japan showed a burned-out picture: few active areas of neuronal, axonal or myelin destruction with the remaining neurons appearing surprisingly healthy.

A significant number of PD cases were found to show not only lower motor neuron involvement but also severe pelvicrural flexion contractures in the advanced stage of the disease. This observation presents an important question of: (1) motor neuron involvement as a part of the natural history of chronic diseases of the CNS, or (2) a process identical to ALS which occurs in the same patient. If the latter is true, these cases may represent a continuum of ALS and PD, and thus indicate a single etiology of these two diseases.

TAB 8.C — NEUROTOXICOLOGY SECTION, ODIR -- ODIR(NTS)

ANNUAL REPORT

1 OCTOBER 1982 THROUGH 30 SEPTEMBER 1983

Neurotoxicology Section, ODIR
National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

ANNUAL REPORT
October 1, 1982 through September 30, 1983

Neurotoxicology Section, Office of the Director

National Institute of Neurological and Communicative Disorders and Stroke
Richard L. Irwin, Chief

SUMMARY

1. In Vitro Studies of Erythrosin B Neurotoxicity. We have previously reported that erythrosin B: 1) blocks synaptosomal uptake of dopamine; 2) inhibits Na,K-ATPase in rat brain; 3) inhibits the high affinity binding of the cardiac glycoside, ouabain, to Na,K-ATPase; 4) interacts with rat brain cortical membranes in a "receptor-like" manner at a site distinct from the cardiac glycoside binding site. Our most recent data indicate that erythrosin B inhibits: 1) not only high affinity [^{3}H] ouabian binding in brain tissue but also low affinity [^{3}H]ouabain binding in rat brain tissue; 2) both Type I and Type II [^{3}H]ouabain binding to rat brain cortical tissue; 3) inhibition by erythrosin B is not limited to brain ATPase activitiy. It also inhibits lamb kidney Na,K-ATPase. Light-induced increases in the inhibitory potency of erythrosin B are dependent on both ouabain concentration and duration of incubation of the tissue with [^{3}H]ouabain and erythrosin B. Studies are in progress to delineate the generalities and the specificities of the binding of erythrosin B to rat cortical membranes. Purification steps and variations in incubation conditions will be explored further in order to elucidate a possible "receptor" for erythrosin B in rat brain tissue preparations. Studies to elucidate the differences in the inhibitory processes involved in the light-induced vs. light-protected inhibition of [^{3}H]ouabain by erythrosin B are in progress.

2. Central Nervous System Variability and Sensitivity to Neurotoxins. We have demonstrated both quantitative and qualitative differences in the catalytic activity of Na,K-ATPase and [^{3}H]ouabain binding to crude cortical membrane preparations from brains of rats of different ages. Variable response to erythrosin B by brain cortical membrances from different ages of rats will be examined using the age-specific differences we have found in Na,K-ATPase catalytic activity and ouabain binding. Clarification of the functional importance of the lipid composition and/or the myelin content of cortical membrane preparations to ouabain binding and erythrosin B binding is being studied by myelin purfication methodologies, delipidation procedures, and the study of brains from mutant rodent strains characterized by myelin degeneration.

Idiopathically, obese humans have been demonstrated to have lower Na,K-ATPase activity in red blood cells than do normal individuals. We have examined a rat strain with a mutation for obesity to determine whether these mutants have altered brain Na,K-ATPase which we could exploit as a useful tool to investigate the actions of ouabain and erythrosin B on brain Na,K-ATPase activity. Recent evidence suggests that obese and lean rats of the LA strain have equivalent levels of brain Na,K-ATPase when optimal levels of magnesium are present but variation in magnesium ion distinguishes lower level of Na,K-ATPase in obese rats. We are studying the effect of high sucrose vs. high starch diet on Na,K-ATPase in these unusual animals. Variable levels of ATPase activity due to the obesity mutant in the LA/N rat strain will be examined for unusual response to erythrosin neurotoxicity.

3. Interactions Between Cholecystokinin and Dopamine Receptors. We have demonstrated a slight modulation of high affinity [^{3}H] spiperone (a dopamine agonist) binding to striatal dopamine D_2 receptors in neuronal tissue prepared from the caudate of rat brains. Presently, we are studying the dose-response relationship for alteration in [^{3}H] spiperone binding by CCK. Expansion of this investigation will include studying the effects of CCK, analogues of CCK and fragments of CCK on high affinity [^{3}H] spiperone binding, and also will include studies of other dopamine receptors. The behavioral effects of these compounds will be studied using the Ungerstedt animal model of Parkinson's disease. These projects have clinical relevance to the neurological disorders of Parkinson's disease.

4. Anticonvulsant Drugs, Seizure Disorders, and Specific Adenosine Receptors. We have used an in vitro assay measuring the characteristics of neuronal adenosine receptors using [^{3}H]cyclohexyladenosine, an adenosine agonist, to bind to rat brain tissue. Tegretol powerfully inhibits the binding of [^{3}H]cyclohexyladenosine to the adenosine A_1 receptor. The influence of GTP on the interaction of Tegretol with the adenosine A_1 receptors in the CNS does not imply a strong agonist activity. Phenobarbital and dilantin have marginal effects on the adenosine A_1 receptor. Natural methylxanthines inhibit the binding of [^{3}H]cyclohexyladenosine to rat brain adenosine A_1 receptors.

Seizure disorders, either of iodiopathic etiology, drug induced, or of multiple other etiologies, are a major cause of neurological dysfunction. Our studies will promote a better understanding of the convulsant and anticonvulsant properties of drugs. These studies should clarify the direction for further biomedical research and lead to therapeutic improvements. Our present data on the interactions of methylxanthines and anticonvulsant drugs with the adenosine A_1 receptor are measurements which result from the combined effect of these drugs on both the higher affinity and lower affinity [^{3}H]cyclohexyladenosine binding sites. WE are beginning an investigation of a differential response between these two apparently different binding sites and methylxanthines and anticonvulsant drugs.

5. Exocytosis Modelling: Kinetics of Membrane Aggregation and Fusion. Release of neurotransmitters and neuromodulators from their storage organelles takes place by exocytosis, a process in which the influx of calcium into the cell or nerve terminal triggers the fusion of the storage granule with the cell plasma membrane. The membrane fusion events can be modelled by studying the calcium-promoted fusion of artifical and biological membranes with each other.

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. The machine can presently acquire data from three different photomultipliers. A new version of the machine will be able to acquire four channels of data from material excited by two different wavelengths of light.

We have previously demonstrated by stopped-flow mixing techniques that the aggregation of small vesicular structures (artificial lipid vesicles, neurotransmitter storage granules, etc.) can be described as the sum of several bimolecular rate reactions. We have extended this work to investigate the fusion of these particles using stopped-flow acquisition of the progress of fluorescence-resonance energy transfer (FRET) signals from donor and acceptor phospholipids inserted in the membrane bilayers. The membranes are rapidly mixed with calcium

and/or other agents which promote membrane fusion and the reactions are followed by the relaxation of the turbidity and FRET signals. The rate-limiting step for fusion of these vesicles is aggregation itself. Small unilamellar vesicles with a high radius of curvature leak profusely during fusion while larger vesicles with less radical changes in surface curvature do not. We ascribe the leakiness to defects in the packing structure of the membrane phospholipids.

6. 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, CNB, NIMH, demonstrate that at physiological osmotic pressures the catecholamine and ATP 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 FRET between granule membrane proteins labelled with fluorescent maleimides. 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.

Fluorescently-labelled lipid probes have been successfully inserted into chromaffin granule membranes. FRET studies of calcium-promoted fusion of these membranes show that fusion also runs 5-10 fold more slowly than aggregation. These results imply that substantial rearrangement of the protein and lipid components of the membrane is required for fusion to occur.

We have been investigating the hypothesis that the neurotoxicity of heavy metals such as lead and tin may be due to interference with the calmodulin control of calcium-dependent cytoskeletal structures. Recent results demonstrate that the chromaffin-granule membrane contains several calmodulin binding proteins and that the calcium-promoted fusion of artificial lipid vesicles with chromaffin granule membranes may be under calmodulin control. A soluble calcium-specific protein (synexin), isolated from chromaffin tissue or liver, enhances the ability of calcium to aggregate chromaffin granule membranes. However, synexin has the same effect on mitochondrial membranes, microsomes and negatively charged artificial membranes. We have recently isolated a second protein (synexin II) from adrenal medulla and liver with entirely different molecular weight, protease susceptibility and peptide fragments, suggesting that the aggregation phenomenon is best regarded as a convenient method for discovering calcium specific proteins.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02264-07 ODIR

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Animal Models of Neurological Disease

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Sally M. Anderson, Expert, Neurotoxicology Section, NINCDS

COOPERATING UNITS *(if any)*
Experimental Therapeutics Branch, NINCDS; Carbohydrate Nutrition Laboratory, Beltsville Human Nutrition Research Center, USDA

LAB/BRANCH
Office of the Director, Intramural Research Program

SECTION
Neurotoxicology Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.0	1.0	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is the investigation of basic mechanisms associated with naturally occurring or artifically neurotoxin-induced neurological diseases through the use of animal models and in vitro experiments. Interactions of various neuroactive drugs and neurotoxins with neurotransmitters in the central nervous system 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: A) to define populations of individuals that may be at increased risk to neurological disease resulting from exposure to neurotoxins and B) to use naturally occurring variability in central nervous system function, anatomy and/or neurochemistry, to elucidate mechanisms of actions of neurotoxins. Several different projects have been investigated this year. (1) Interactions of the artificial food color, erythrosin B, with neuronal membranes and neurotransmission have been studied. Erythrosin B has been demonstrated, by several different criteria, to be a potent inhibitor of ATPase activity in brain and other tissues. Its inhibitory potency can be enhanced in vitro by exposing the tissue-erythrosin B complex to light. Studies are in progress to elucidate a possible "ligand-receptor" interaction between ATPases and erythrosin B. (2) Genetic and age variation in brain Na,K-ATPase are being investigated because they present a potential tool for elucidating the actions of erythrosin B on brain Na,K-ATPase. (3) Neuronal interactions between neuropeptides and dopamine D2 receptors in the basal ganglia are being studied to increase our understanding of the functional significance of dopamine defects in patients with Parkinson's disease and the therapies necessary for alleviation of their symptoms. (4) We are studying the effects of anticonvulsant drugs on adenosine A1 receptors to promote a better understanding of the actions of convulsant and anticonvulsant drugs. This new information should point out new directions for further biomedical research and lead to therapeutic improvements for these diseases.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02451-03 ODIR

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Cellular and Molecular Approaches to Neurotoxicology

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Stephen J. MOrris Expert Consultant NTS NINCDS

COOPERATING UNITS *(if any)*
BEIB, DRS; LTB, NCI; Dept. of Pharmacology, Univ. of Miami Medical School

LAB/BRANCH
Office of the Director, Intramural Research Program

SECTION
Neurotoxicology Section

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

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.25	1.0	0.25

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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 (CG), and its inhibition by various heavy metals, are being studied as model processes for exocytotic release of catecholamines in vivo.

The kinetics of calcium-promoted aggregation and fusion of the granules can be followed using fluorescence resonance energy transfer (FRET) techniques. The effect of calcium on granule membrane proteins labelled with fluorescent maleimides has directly demonstrated the fluid mosaic nature of the granule membrane. Calcium promotes FRET which is due to the aggregation of the membranes. This component runs with a rate which is 5-10 times slower than aggregation itself. Fluorescently-labelled lipid probes have been successfully inserted into chromaffin-granule membranes. FRET studies of calcium promoted fusion of these membranes show that fusion also runs 5-10 fold slower than aggregation. These results imply that substantial rearrangement of the protein and lipid components of the membrane is required for fusion to occur.

Heavy metal neurotoxicity may operate by interference with calcium-controlled cell processes. A soluble calcium-specific protein (synexin), isolated from chromaffin tissue or liver, enhances the ability of calcium to aggregate chromaffin-granule membranes. However, synexin has the same effect on a number of biological and artificial membranes which is related to their net negative surface charge. We have isolated a second protein (synexin II) from these sources with entirely different molecular weight, protease susceptibility and peptide fragments, suggesting that the aggregation phenomenon is best regarded as a convenient method for discovering calcium specific proteins. The chromaffin granule membrane contains several calmodulin binding proteins and the calcium-promoted fusion of artificial lipid vesicles with CG membranes may be under calmodulin control.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02525-02 ODIR

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Exocytosis Modelling: Kinetics of Membrane Aggregation and Fusion

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Stephen J. Morris Expert Consultant NTS NINCDS

COOPERATING UNITS *(If any)*
CNB, NIMH; LTB, NCS; LPD, NIAID; Dept. of Biochemistry, Cornell Univ.; Dept. of Anatomy, Duke Univ.; Dept. of Pharmacology, Univ. of Miami.; Dept. of Endocrinology, Univ. of Texas Medical School, Houston.

LAB/BRANCH
Office of the Director, Intramural Research Program

SECTION
Neurotoxicology Section

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

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.3	1.4	0.9

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The release of neurotransmitters, neuromodulators and hormones from synapses and neurosecretory cells involves exocytosis: the fusion of the storage granule membrane (synaptic vesicle, chromaffin granule, neurohypophysial granule, etc.) with the cell plasma membrane. We have chosen to examine the divalent metal ion-promoted fusion of both artifical and biological membranes as models for the reactions involved in the cellular processes.

The kinetics of membrane fusion reactions in a model system consisting of sonicated phospholipid vesicles are being studied using a computer-controlled, multisignal, stopped-flow, rapid-mixing apparatus. Membranes labelled with fluorescent phospholipids are rapidly mixed with calcium and/or other agents which promote membrane fusion, and the reactions are followed by the relaxation of several optical signals. The machine can presently acquire data from three different photomultipliers. A new version of the machine will be able to acquire four channels of data from material excited by two different wavelengths of light.

Initial results demonstrate that the rates of fusion of both small unilamellar sonicated phospholipid vesicles (SUV's) and larger unilamellar vesicles formed by reverse phase evaporation (REV's) are limited by the aggregation of the vesicles. Fusion of REV's results in little to no loss of materials stored in the vesicle lumens, while the rapid loss of materials from the SUV's suggest that they are poor models for the biological processes.

Methods for placing the fluorescent phospholipid probes into biological membranes have been developed, which will allow the study of the fusion processes of these particles.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02452-03 ODIR

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Hormones and Central Neurotransmitter Function

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Robert E. Hruska, Senior Staff Fellow, Neurotoxicology Section, NINCDS

COOPERATING UNITS *(if any)*

NONE

LAB/BRANCH

Office of the Director, Intramural Research Program

SECTION

Neurotoxicology

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 *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been discontinued because of the departure of the principal investigator.

ANNUAL REPORT

October 1, 1982 - September 30, 1983

Instrumentation and Computers Section
National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

ANNUAL REPORT

Instrumentation and Computers Section

National Institute of Neurological and Communicative Disorders and Stroke

October 1, 1982 - September 30, 1983

The Instrumentation and Computers Section provides technical support for investigators of NIMH and NINCDS IRPs 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 Computers 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 225 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.

(a) Monitor. The major hardware advance this year was the introduction of a new PAM which stores 10 days of data, with 15 minute resolution, and is half the size of its predecessor. The new PAM utilizes small-outline plastic packages for logic circuits, and leadless carriers for memory circuits. All parts are readily available and inexpensive. Assembly is performed by a contractor; yet the total cost of the new PAM is half that of the old device. The Section is preparing to produce the new PAM in large quantities, with the goal of replacing all old models within the next year.

(b) Telecommunications. This project involves the development of a PAM data telecommunications system, which will allow data to be transmitted to the Section's VAX computer via telephone, from anywhere in the country. The subject will have a microprocessor-based device in his home; it will accept the PAM, read the data, dial the phone number for the VAX, establish communication, transmit the data, clear and reset the PAM. Local software will put the data in the subject's continuous file. A prototype device is now being tested, but the software development is incomplete.

(c) Test/Initialization Instrument. In addition to reading, storing, and analyzing activity and temperature data, the PAM readout minicomputer has been used to perform several routine test and initialization procedures on the activity monitors. Since it would often be more convenient to perform these procedures in the wards or clinics, a small handheld instrument has been developed for use with the new PAMs. Responding to pushbutton commands, the instrument can: (1) display the PAM battery voltage and indicate its condition; (2) initialize each of the 1024 PAM memory locations to a value of zero and give an error message if any location fails to initialize; (3) initialize the PAM memory address pointer to the first memory location; and (4) read and display the first 32 activity values contained in the PAM. In order to realize these functions in a portable, battery-powered instrument, a CMOS microprocessor and support chips were used.

(2) Data Acquisition System for Isolation Rooms. The design of a computerized data acquisition system for two patient-isolation rooms has been completed. This system allows the study of biological rhythms and the cyclic nature of certain mental illnesses by monitoring human subjects who are isolated from all time cues. Periodic reading of temperature and activity from the subjects are obtained through electrically isolated signal conditioners. These data values, along with average room illumination readings, are converted to serial digital data and transmitted over a two-wire link to a minicomputer storage and display system. The data are reformatted into the PAM continuous file structure and on-line hard-copy of the three measured parameters is generated. A second design phase will

incorporate touch-input CRT terminals for patient mood self-ratings and patient-staff communications.

(3) EEG Amplifier System. The design has been completed and construction begun on a new 32-channel EEG amplifier system. The design incorporates several new integrated circuit components and printed circuit board layouts to permit construction of a compact, low-cost-per-channel unit. The system will be used for several ongoing research projects including topographic brain mapping. The simplified construction and small size will permit expansion to a 64-channel system in the near future.

To facilitate the use of the EEG system on different computers with different A/D input requirements, the unit was made as flexible as possible. For example, a new type of filter is available (switch capacitive) and was incorporated in the design. The switched capacitor filter requires an input clock which sets the cut-off frequency of the filter; however, this is not a limitation in that varying bandwidth requirements for different experimental situations can be accommodated by selecting different input clock frequencies.

Sample and hold modules are also incorporated in the design to prevent "skewing" errors associated with sampling a large number of channels. The sampling frequency can also be varied as needed, and front panel switches allow the user to switch the filters or sample and holds in or out as desired.

The 32 data channels are also multiplexed into a 16-channel output for use with the Grass polygraph.

(4) Discriminator and Iontophoresis Systems. Five ICS amplitude/time window discriminator systems were completed this year. The use of CMOS logic and the recently redesigned printed circuit boards allow the units to be versatile and reliable. The versatility of the design allows each unit to be tailored to the needs of the requestor. Several discriminators were built with tone generators, and one included a special post stimulus, adjustable time window. In addition, a printer interface designed around a small Datel printer is available. Also, two modified units for processing post-synaptic potentials were completed this year. Four ICS 5-channel iontophoresis systems were also completed and are currently being used in neuropharmacological studies in the IRP.

(5) Neurophysiological Data Preprocessor. A microprocessor system is being developed to replace the custom logic circuitry used by the present Laboratory of Neurophysiology Data Acquisition System. The new preprocessor will record the times of occurrence of 64 different events and 8 different pulses. This information will be transmitted to the central processor through a parallel interface and the information will be coded in such a form as to ensure compatibility with the present software that is used for analysis and display of the data. The preprocessor will decrease response time to events and pulses, and free the central processor for experiment control.

(6) Neuro-PET Scanner Chair and Gantry Controller. A controller for the gantry and electromechanical chair was designed and installed into the Neuro-PET Scanner, which was developed by NINCDS in conjunction with BEIB. The controller has facilitated the positioning of eighty-one (81) patients in the ring of the scanner. The design of the controller includes a digital readout of the exact position of the head of the patient and various safety stops to ensure patient and machine safety.

(7) Visual Evoked Response Stimulus System. A visual evoked response stimulus system has been built, that will randomly select one of eight 35 mm slide images and project it on to a 35 cm x 50 cm 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 RS 232 serial interface.

(8) Conference Room Microphone System. The versatility of the Building 36 conference room public address system was increased by implementation of an audio summing amplifier interface that allows up to 12 inexpensive lapel microphones to be used around the conference room table. The lapel mikes were also adapted for use by speakers using the podium.

(9) Four-Arm Radial Rat Maze. An elevated multi-level, 4-arm radial rat maze was designed, constructed, and installed to assess the effects of neuropeptides on learning, memory and perception in laboratory rats. Audible and/or visual cues are 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 is dispensed. At the end of the testing period, statistical data is printed regarding the animal's performance. An eight-bit microprocessor single-board computer is used to monitor and control the maze and perform the statistical calculations.

COMPUTERS

Small computers are ideally suited for laboratory research in neurophysiology and psychology. They are used in the laboratory for on-line, real-time interactions, process control, and data acquisition. Recorded data may be stored, combined with other data, reduced statistically, transferred to larger computers for further analysis, transformed for presentation graphically or mathematically, and the results may be printed or plotted. Increasing use is being made of the small computer for processing the text of scientific papers and communications. Data base management is now available for the small computer, as are limited management information systems.

Techniques have been developed for image processing which are applicable to many diverse experimental systems, ranging from autoradiographs of brain tissue sections to the analysis of two-dimensional electrophoresis gels.

Larger mini-computers, the so-called super-mini's, have been reduced in price and are now available for functions formerly performed by larger time-shared systems. These systems allow applications in modeling, curve fitting and statistical treatment that would be prohibitively expensive on large systems.

Inexpensive personal computers are proving useful for dedicated applications. Many scientists are developing software for these computers, which they offer to the scientific community at low cost. PCs will become increasingly useful in the laboratory and their potential should be exploited.

Microcomputers incorporated in the design of biomedical instrumentation provide a savings in design and fabrication time for instruments, and a more flexible system than one based on discrete components.

The Instrumentation and Computers Section is actively involved in the applications of small computers in the IRP. By integrating the functions of biomedical instrument design and laboratory computer systems with software designed specifically for the research community, the Section offers computer support services for a broad range of scientific disciplines.

LABORATORY COMPUTERS

The design goal for the laboratory instrument computer is to provide maximum function, tailored to the specific experimental design, with minimum cost. ICS provides consultation on the specification and selection of laboratory computers for new applications; conducts systems studies in collaboration with the scientist; and helps the scientist in the procurement, installation and maintenance of the equipment.

In support of these efforts, ICS maintains two support computers, one in Bldg. 36, and one in the Clinical Center. These systems provide the more expensive equipment necessary for off-line data storage, efficient data processing, communications with DCRT computers, and plotting and printing of the data. The systems are run on an open shop basis and are used for program development, training, and testing the feasibility of new systems for the laboratories.

TRAINING AND SOFTWARE SUPPORT

ICS provides training for the scientist or support personnel who will be programming and maintaining the system. Personnel limitations make it impossible for ICS to provide applications programming, so such programming must be supplied by the laboratory. ICS computer personnel are always available for consultation, training and help in debugging, as well as assistance in the selection of part-time programmers or consultants. Commercial software packages or applications from other research labs are often available, and ICS will evaluate such systems.

ICS maintains a library of procedures which were written specifically for the laboratory computers used in the intramural community. These procedures are designed to be incorporated into the users' programs. In addition, ICS will aid the investigator in writing the difficult time and data dependent sections of real-time programs.

PERSONAL COMPUTERS

Personal computers have the potential to become powerful and useful laboratory computers. ICS is conducting a study of the different models for future use in the laboratory. Manufacturers are offering increasingly sophisticated word-processing packages, and they may replace some of the commercial word-processors now being rented. Other software packages provide data base management, management information systems and spread sheet accounting.

In the near future, hardware and software should be available to incorporate these systems into a network, tying them into the larger computers of the IRP. Integrating these systems will provide a cost effective utilization of equipment for laboratory and administrative personnel.

PROGRAM MAINTENANCE

There are now more than 60 minicomputers in the program; many of these systems have been in use for years. The programs used on these systems were written by a number of people, many of whom are no longer in the IRP. Design of these programs is such that changes are usually required as the experimental protocol develops, so program maintenance is a continual, and time-consuming function of the Section. Structured programming techniques and standardization of equipment have enabled the Section to provide these services without an increase in personnel.

MICROPROCESSORS

The Section also maintains a microprocessor development system for the software and hardware development of microprocessor-based instrumentation at both the chip and single board computer level. The system currently supports three common microprocessors; one 16-bit processor, and two 8-bit processors.

IMAGE PROCESSING SYSTEM

The ICS maintains a general purpose image processing system consisting of an Optronics rotating drum film scanner, a DeAnza image array processor, and a PDP-11/60 computer. Images to be processed may be obtained by scanning autoradiographs, x-ray film, or photographic negatives, or by using images generated by CAT or ECAT scanners. A camera station is available to generate color hardcopy using Polaroid SX-70 or 35 mm film.

Interactive, menu-driven, software packages have been developed to provide an extensive and expandable repertoire of basic image processing 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. The two primary applications of the system are the densitometric analysis of autoradiographs of brain or tissue sections and the analysis of two-dimensional electrophoresis gels. The software currently available on the PDP-11/60 based system is being converted to run on the multi-user VAX-11/750 computer which is managed by the Section.

VAX COMPUTER SYSTEM

The Section manages a multi-user VAX-11/750 computer system that is available for use by all investigators in the IRP. The VAX is located in Bldg. 36, in space furnished by the Laboratory of Cerebral Metabolism, NIMH. Potential users in Bldg. 36 may request installation of hard-wired cable connections, or the VAX may also be used on a dial-up basis.

The primary use of the VAX is for image processing applications. A high resolution color image display is now operational and an Optronics film scanner directly connected to the VAX will be available in the near future. In addition,

an Ethernet link is being developed to allow high-speed transfer of images between the VAX and the existing PDP-11 based image-processing systems.

A device-independent graphics package has been developed on the VAX that permits plots to be generated on numerous display terminals and hardcopy devices. A terminal emulation program is available which permits small laboratory computers to function as graphics terminals when using the VAX, as well as supporting file transfer in both directions.

The SPICE2 circuit analysis program has been installed on the VAX and is being used by several investigators for modeling neuronal circuits. Programs have been written to generate graphical displays and hardcopy plots of the output of the SPICE2 program.

OTHER APPLICATIONS

(A) Neurophysiological Data Analysis System. This system has been used extensively by laboratories in NIMH and NINCDS. It relates neurophysiological data such as neural events of the EMG with behavioral events related with learning, discrimination, perception, etc. The system provides visual presentation of the data, relating all events in time. The system was extended to allow further selection from the data, sorting the data on criteria derived from analysis of time dependent areas of the data, and further statistical analysis of the data. An improved data acquisition system is currently being designed; this will require rewriting the data acquisition programs. The resulting system will enable the investigator to add elements utilizing the computer in the control of the experiment and presentation of the stimuli.

(B) Rat Motion Cages. The rat motion cages developed by the Section for the Adult Psychiatry Branch, NIMH, will be used to measure epileptic seizure activity in rats. The animals will be maintained in the cages for long periods of time to measure the effectiveness of proposed treatments on the diminution of seizure activity.

ENGINEERING, COMPUTER AND FABRICATION SERVICES

This table shows the distribution of the Branch's workload among the various laboratories and branches. We have listed only the major users. .

LABORATORY OR BRANCH	HOURS	PERCENT
Clinical Psychobiology, NIMH	4513	14.54
Biological Psychiatry, NIMH	3614	11.66
Neurophysiology, NINCDS	3044	9.81
Clinical Science, NIMH	2761	8.97
Neurophysiology, NIMH	2359	7.60
Psychology and Psychopathology, NIMH	2231	7.19
General and Comparative Biochemistry, NIMH	1467	4.73
Cerebral Metabolism, NIMH	1410	4.54
Neuropathology and Neuroanatomical Sciences, NINCDS	1370	4.42
Adult Psychiatry, NIMH	1254	4.04
Neuropsychology, NIMH	887	2.86
Surgical Neurology, NINCDS	865	2.79
Neurochemistry, NINCDS	831	2.68
Molecular Biology, NINCDS	674	2.17
Biophysics, NINCDS	486	1.57
Experimental Therapeutics, NINCDS	390	1.27
Neurochemistry, NIMH	343	1.11
Molecular Genetics, NINCDS	232	.75
Neural Control, NINCDS	179	.58
Neuro-Otolaryngology, NINCDS	171	.55
Developmental Psychology	107	.35
Clinical Neuroscience, NIMH	76	.25
Central Nervous System Studies, NINCDS	63	.20
Infectious Diseases, NINCDS	58	.19
Neuroimmunology, NINCDS	57	.18
Service on Committees	923	2.97
*NIMH (Total)	21,125	67.76
*NINCDS (Total)	8,540	27.39
*NICHD (Total)**	1,512	4.85
	31,177	100.00

*These figures represent our total effort; they include time for labs not listed individually.

**NICHD loans the Branch one position, and is thus entitled to 1700 hours of service.

ANNUAL REPORT
October 1, 1982 through September 30, 1983

Laboratory of Biophysics
National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

Annual Report
October 1, 1982 thru September 30, 1983
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 (LB) is concerned with investigating molecular and cellular mechanisms responsible for excitation, membrane potentials, the generation of the nerve impulse, synaptic activity, axoplasmic and neuroplasmic transport, 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, Massachusetts. The Woods Hole Unit is composed of 2 sections: the Section on Neural Membranes (NM) and the Section on Neural Systems (NS). The Bethesda unit of the laboratory is made up of the Section on Molecular Biophysics (MB).

The Laboratory of Biophysics has focused 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, 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. This approach adopted biophysical methods integrated with modern ultrastructural and biochemical techniques to study 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 approach.

At present, the Section on Molecular Biophysics studies 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 and axoplasmic transport mechanisms 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.

The Laboratory of Biophysics operates over a broad 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 Laboratory's 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.

Voltage-gated, sodium-ion channels are responsible for the regenerative conductance changes associated with the rising phase of action potentials in many excitable membranes. Existing models of channel gating kinetics involve conductances that are continuous functions of time for large numbers ($\gtrsim 10^4$) of individual channels. Further, discontinuities in the first derivative of the conductance time course occur only at repolarizing voltage-clamp steps. This study showed that the sodium conductance itself can undergo rapid transitions that can be considered discontinuous on the temporal scales normally associated with gating. Such "instantaneous" conductance changes may have implications for the type of molecular transitions associated with channel gating.

In another study the sodium conductance was shown to undergo rapid changes during certain repolarizing voltage clamp steps at least partially in the gating range. The shift in conductance increases with time of depolarization from approximately zero to $\sim$ 25 to 30% at 7 milliseconds for a potential step from +70 to -30 mV. Conductance shifts were also observed for voltage steps from various depolarized levels to -70 mV. All observed shifts were in the direction of a decreased conductance. The shifts appear to be weak function of the concentration of external calcium, which also acts as a voltage-dependent channel blocker for inwardly directed sodium currents. The phenomenon suggests the presence of voltage- and time-dependent molecular processes which do not themselves yield open or closed channel conformations, but which affect the magnitude of the rate constants that do connect open and closed state conformations.

Another study of the sodium channel showed that sodium currents of 16 to 20 ms duration occur at -80 mV following brief hyperpolarizing pulses in squid axons perfused internally with relatively low internal ionic strength solutions and externally with a relatively low calcium (< 10 mM) solution. The magnitude of the current is a function of duration of the prehyperpolarization (0.7 to 5 ms) and its voltage (-100 to -150 mV). The maximum observed conductance was 1.7 mS/cm^2 with $[Na]_i$ = 50 mM. Conditional gating kinetic schemes were derived to account for the phenomenon.

The anticonvulsants ethosuximide and valproate are evaluated and compared in their action on the gating and permeability of the excitable Na- and K-channels of the squid giant axon. The drugs are highly specific with regard to channel and membrane side of application. Both drugs when applied internally affect the Na channel activation gating in ways that lead to the conclusion that they do not also act as channel blockers. However, external ethosuximide is clearly a

voltage-independent Na channel blocker with no effect on channel gating. On the K channel, ethosuximide appears to have a mixed action affecting both gating and the ion flux through open-gate channel molecules. However, valproate slows K channel gating without effect on flux through open-gate channels.

Potassium ion current in squid axons is usually modified by the effects of ion accumulation in the periaxonal space during voltage clamp depolarization. The time course of potassium channel activation and ion accumulation usually overlap. A widely accepted procedure for circumventing the effects of accumulation in measurements of activation kinetics consists of measuring the difference in the current at the end of a depolarizing pulse and immediately following return of the membrane potential to the holding level. This instantaneous jump procedure is based upon the assumptions that the potassium channel current voltage relation (I/V) is a linear function of the driving force, and that the IV and the potassium channel gating kinetics are both independent of ion accumulation. The later assumption appears to be appropriate for activation kinetics. However, both assumptions concerning the I/V are incorrect, in general. Consequently, the jump procedure provides a misleading view of gating kinetics for membrane depolarizations which produce significant net current. Depolarizations which produce little or no current indicate that the Hodgkin-Huxley n^4 model of potassium channel kinetics is appropriate for the physiological range of membrane potentials.

Cesium ions block potassium channels in biological membranes in a voltage-dependent manner. For example, external cesium produces little or no block of outward current, a slight block of current when the membrane potential, V, is close to the potassium equilibrium potential, E_K, and a marked block of inward current for $V << E_K$. These effects produce a characteristic N-shaped current-voltage relationship. These results were modeled by single file diffusion of ions in a narrow channel spanning the membrane with a special blocking site in the channel for cesium ions. The model leads to detailed comparisons of the effects of cesium on potassium channels in different types of biological membranes.

Another study showed that the nerve impulse could be derived directly from the summation of single channel unit conductances demonstrating the continuity between microscopic and macroscopic conductance domains.

The Hodgkin-Huxley model for the nerve membrane action potential can be described in terms of channels and gates. Ions permeate the nerve membrane through narrow ion specific pores, or channels, which are modulated by a voltage-dependent gating process. The model provides a detailed kinetic scheme for channel gating, but not for channel permeating. Radioactive tracer flux experiments suggest that permeation occurs via single file motion of ions through a channel. This process has been modeled as a random walk with internal states. The theory leads to expressions for one-way fluxes which can be compared with experimental tracer flux data. Recent experiments on channel gating have indicated that the Hodgkin-Huxley model of the gating process requires certain modifications. A class of modifications has been derived involving temporal memory of gating and interactions between gating particles of any single channel.

A study of the effects of the calcium antagonists, verapamil, D-600 (methoxyverapamil), and nifedipine on ionic channels in the internally perfused squid giant axons was performed under voltage clamp conditions. These results in conjunction with other studies suggest that D-600 and the other related compounds are selective blockers of calcium channels in squid axons.

Studies comparing the electrical activity of ionic channels in heart cells with comparable channels in nerve continued at a high pace. These studies have added to our knowledge of spontaneous and repetitive activity in both neural and cardiac tissue.

Development of methods and systems for the study of neural function and structure has continued within the section. The Section on Neural Membranes has developed a number of data acquisition systems to collect data from various types of electrophysiological equipment, electron and light microscopes, as well as other experimental equipment used by other sections as well as NM. Data may be processed locally or transported to a host PDP-11/60 via direct connect lines and/or magnetic media. The PDP-11/60 is connected remotely to a VAX/780 and a DEC-10 system via two modems enabling LB to use the resources of these larger systems.

It is now 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 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.

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. The section continues to generate 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. These studies 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.

In addition to conducting rapid impulses to activate muscle tissue, nerve cells synthesize many materials necessary to the maintenance of their structure and function. As diffusion is a very slow process, the term "axoplasmic transport" is used to describe intracellular particle and organelle movements. Though much slower than a nerve impulse, these movements exceed the rates generally associated with passive diffusion. The Section is visualizing the structure or structures involved in this kind of transport by using electron microscopy. We also are interested in seeing actual movement in living cells, using traditional light microscopy, and in correlating these movements with the underlying structures that might be responsible for or associated with this transport.

A variety of methods has been used to study the movement of organelles and particles inside nerve fibers. Most of these methods use video cameras to

capture images of living material under microscopes, then enhance these images, and present them in electronic form for storage on magnetic tape. With the video enhanced light microscope it is possible to see the movement of mitochondria, large vesicles, and other particles. The observed particle movements usually run parallel to the long axis of the nerve fiber. Several different rates exist for these movements in single squid giant axons, and there are different kinds of movement, ranging from smooth-flowing to oscillatory. Axoplasmic transport even proceeds in extruded axoplasm, leading us to infer that this transport does not necessarily depend on the electrical activity of the nerve membrane. Cross-bridge activity between neurofilaments and neurotubules appears to be responsible for organelle and particle movement. The exact nature of the cross-bridge action remains unknown at this writing. Several possibilities are under investigation: 1) cyclic attachment and detachment of the bridges to highly specific sites on the organelles and particles, producing motion in a rachet-like manner; 2) ballistic impelling of organelles and particles with the cross-bridges beating in a manner similar to cilia; and 3) a transport filament hypothesis. Regardless of which of these mechanisms is correct, it is clear that adenosine triphosphate (ATP) is required as an energy source for activity and that divalent ions, such as Ca^{++}, have a role in activating the mechanism. The mechanism(s) must also account for movement of different particles in different directions, with different rates.

In addition, the Section has been able to demonstrate fast axonal transport in reactivated squid axons that had been preserved in glycerol at $\sim -5^{\circ}$ for several weeks. Both ortho- and retrograde particle and organelle movements were observed in these resurrected axons that were indistinguishable from axonal transport in freshly excised axons.

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 an opportune preparation for this investigation. It has been possible to determine with Hermissenda a behavioral model of associative learning with many of 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, savings, 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 receptors, interneurons, and motoneurons involved in this neural integration, membrane changes of specific neurons, e.g., Type B photoreceptors, 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 and thereby 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 motoneurons, and ultimately, retarded positive phototaxis. During cumulative depolarization produced by repeated pairings of light and rotation, intracellular Ca^{++} is elevated.

During the past year several experimental findings provided greater insight into how a neural system can undergo long-lasting transformations which encode for associative learning. Identified neurons were found to undergo intrinsic membrane changes which were complimentary to each other as determined by the sign of their synaptic interactions. Evidence was obtained that it is the change of relative rather than absolute excitability which is crucial to the learning process. Other experiments revealed the presence of two additional membrane currents, a voltage-dependent Ca^{++} current and a Ca^{++}-K^+ current, within those identified neurons which control the learned behavior. These membrane currents change with learning as was previously observed for another voltage-dependent, early K^+ current.

Within the last year it has also been possible to directly monitor the level of intracellular calcium as it causes long-term suppression of specific membrane currents during acquisition of the associatively learned behavior. A biochemical step, activation of a calcium and calmodulin-dependent protein kinase has now been shown to mediate the long-term effects of calcium on membrane conductances. Also in the last year a direct demonstration of the causal role of these membrane changes was accomplished by recording and stimulating intracellularly from individual neurons of living animals and measuring resulting behavioral changes on subsequent days. Finally, investigation of the potential generality of these findings in a nudibranch mollusc was begun by intracellular iontophoresis of the enzyme implicated in the Hermissenda learning into cortical neurons of cats. The production of related membrane changes in these cells suggests the plausibility of cellular mechanisms common to both molluscan and vertebrate conditioning.

These findings, together with data collected in previous years, allows us to propose a causal sequence of cellular steps responsible for the memory of stimuli which occur associated in time. Elevated intracellular Ca^{++} within elements of pre-existing neural systems causes enhanced activity of a calcium and calmodulin-dependent protein kinase and thereby increased protein phosphorylation. Increased phosphorylation of specific proteins ultimately results in reduction of two distinct outward K^+ currents and thus enhanced relative excitability of neuronal elements. This change of relative excitability is in turn responsible for the sequence of neurophysiologic (see above) and behavioral changes necessary for associative learning.

Section on Molecular Biophysics.

The main goal of the Section is to determine the molecular mechanisms underlying the behavior of membrane ionic channels and of drugs that interact with these channels.

A major effort this year was the determination of single-channel properties of both chemically activated and electrically activated channels. The main purpose of these studies was to obtain more detailed information about the kinetics of channel gating. This information, in turn, was used to model the discrete states of the channels, to determine the voltage dependence of the

transition rates between the discrete states, and to explain previous results obtained by macroscopic methods.

The chemically activated channels studied were cholinergic postsynaptic channels of muscle, inhibitory (GABA-sensitive) channels of CNS neurons, and calcium-sensitive potassium channels from secretory cells. The electrically activated channel studied was the sodium channel with the alkaloid neurotoxin batrachotoxin bound to it.

For the cholinergic channel, although there is a unique single-channel conductance, there are two open-state lifetimes, and hence two separate open states with the same conductance. This is true for all agonists tested.

The other chemically activated channels studied and the electrically activated channel studied are all influenced by both chemical and electrical stimuli. For the GABA-sensitive channel, the rate of channel closing was found to increase as the membrane becomes more hyperpolarized. The properties of the calcium-sensitive potassium channel, which depend on internal calcium concentration, thereby depend on the rate of calcium entry and hence on the membrane electric field. The BTX-modified sodium channel, which has the same steep voltage dependence characteristic of normal sodium channels, has other properties caused by the presence of the batrachotoxin molecule. These observations suggest that there is not a clear distinction between electrically excited channels and chemically excited channels, and encourage the hope that there are principles of channel behavior that apply to channels in general.

One candidate for a general channel property is the voltage dependence of the transition rates between discrete states of a channel. For the batrachotoxin-modified sodium channel, we found that the transition rates are exponential functions of voltage. This agrees with previous work in this Section on the EIM (excitability-inducing material) channel in lipid bilayers.

Another property of the batrachotoxin-modified sodium channel that we have determined on the basis of single-channel measurements is that it has at least three discrete states - one open state and two closed states. The specific form of the transition rates between these states suggests that all the channels are never open at the same time, regardless of membrane potential. This finding may explain the observation made in macroscopic voltage clamp experiments that some alkaloid neurotoxins never open all the sodium channels at the same time.

Another macroscopic voltage clamp observation that may be explained on the basis of single-channel measurements is the slow inactivation observed for the calcium-sensitive potassium channel. Our single-channel results suggest that this is based on the decrease in channel opening rate with membrane potential.

In order to improve our ability to obtain useful single-channel measurements, we have developed a mathematical description of the statistical properties of the asymmetric random telegraph signal, which is a useful model for the opening and closing of single channels in membranes. These results should eventually enhance our ability to extract useful information from noisy experimental records of single-channel currents.

Our studies of the mechanism of drug action on channels includes macroscopic voltage clamp measurement as well as single-channel measurements. A

drug that we studied in considerable detail by means of voltage clamp is yohimbine. This drug was selected for further study because of our previous work that showed yohimbine to exhibit very prominent use-dependent inhibition of sodium channels and because we were able to obtain the services of an organic chemist able to synthesize a variety of yohimbine analogs. From our studies of the structure-activity relations of these analogs, we can conclude that the use-dependent effect depends primarily on the quaternary ammonium group at position 4 on the yohimbine molecule and that this group binds to a negative site on the sodium channel.

Another approach which has been of considerable use in determining channel properties is the method of gating-current measurement. We have continued our measurements of gating currents in sodium channels, and have found that after large hyperpolarizing pulses, there is a significant delay in the development of gating current, in agreement with previous observations of delays in the development of sodium ionic currents following hyperpolarization. The delay suggests that there are several discrete closed states of the sodium channel, and that, following hyperpolarization, the channel must pass through these states before it can open.

We have recently obtained evidence for a component of gating current associated with the opening of potassium channels. This opens up the possibility of extending the kind of insights previously obtained by gating current measurements on sodium channels. In particular, it should be possible to obtain information concerning transitions between closed states of the channel, where there are no ionic currents.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 01950-12 LB

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Excitable Membrane Characteristics: Voltage Clamp and Impedance Measurements.

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

W. J. Adelman, Jr. Chief LB NINCDS

COOPERATING UNITS *(if any)*

Marine Biological Laboratory, Woods Hole, MA 02543; McGill University

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 *(Use standard unreduced type. Do not exceed the space provided.)*

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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02087-10 LB

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Function and Structure of Ionic Channels: Ion Interactions and Gating Mechanisms.

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

W. J. Adelman, Jr. Chief LB NINCDS

COOPERATING UNITS *(if any)*

Marine Biological Laboratory, Woods Hole, MA 02543; University of Maryland; Emory University

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 *(Use standard unreduced type. Do not exceed the space provided.)*

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^{++}.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02092-10 LB

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Subcellular and Extracellular Structure Associated with Nerve and Muscle.

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

W. J. Adelman, Jr. Chief LB NINCDS

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 *(Use standard unreduced type. Do not exceed the space provided.)*

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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02273-07 LB

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

An Investigation of Electro-Mechanical Coupling in Excitable Tissues.

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

J. B. Wells Research Physiologist LB NINCDS

COOPERATING UNITS *(if any)*

Marine Biological Laboratory

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 *(Use standard unreduced type. Do not exceed the space provided.)*

This project, divided into two major areas of endeavor, continues the investigation in isolated squid giant axons of electrical responses to mechanical stimulation. These responses were compared to similar responses reported in the literature concerned with mechano-electric transduction processes. The second area of interest addressed the creation and testing of a visco-elastic transmission line model based on the electro-mechanical properties of the squid giant axon experiments.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02151-09 LB

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Information Processing in Simple Nervous Systems

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

D.L. Alkon Medical Officer LB NINCDS

COOPERATING UNITS *(if any)*

Marine Biological Laboratory, Woods Hole, MA 02543; Princeton University; SUNY/Albany; University of California/San Francisco; University of Chicago; University of Vermont

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 *(Use standard unreduced type. Do not exceed the space provided.)*

The principal 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, electron microscopy, automated behavioral monitoring of intact Hermissenda, voltage clamp of identified neural elements. Other methods include mariculture, subcellular fractionation, protein phosphorylation analysis, uptake of neurotransmitter precursors, phosphoprotein characterization and purification, and immunologic protein identification.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02088-10 LB

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Function and Structure of Membrane Ionic Channels

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
G. Ehrenstein Research Physicist LB NINCDS

COOPERATING UNITS *(if any)*
Marine Biomedical Institute, Galveston, TX

LAB/BRANCH
Laboratory of Biophysics, IRP

SECTION
Section on Molecular Biophysics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.4	2.9	0.5

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

We have observed the opening and closing of single batrachotoxin-modified sodium channels in neuroblastoma cells using the patch-clamp method. The single-channel data together with voltage-clamp data on the same system could be accounted for by a 3-state closed-closed-open model, where a closed state refers to a molecular conformation of the channel that does not allow ions to pass and an open state refers to a molecular conformation of the channel that allows ions to pass with a conductance of about 10 pS. Transition rates between the states are exponential functions of membrane potential. One of the implications of this model is that there are always some closed channels, regardless of membrane potential.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02091-10 LB

PERIOD COVERED
October 1, 1982 to September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Mathematical Modeling

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
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:
1.1	1.0	0.1

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Mathematical modeling of the following phenomena was continued:

The nonlinear properties of squid axon membrane using a sinusoidal voltage clamp.

Signal detection and analysis of the square wave currents from single channels opening and closing in a membrane, distorted by noise and low-pass filtering.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02218-08 LB

PERIOD COVERED

October 1, 1981 to September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Effect of Drugs on Voltage-Dependent Ionic Conductance in Membranes

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

D.L. Gilbert Research Physiologist LB NINCDS

COOPERATING UNITS *(if any)*

R. J. Lipicky, Food and Drug Administration; E. Wenkert, Univ. of California, at San Diego; H. Pant, NIH - Alcohol Abuse and Alcoholism

LAB/BRANCH

Laboratory of Biophysics, IRP

SECTION

Section on Molecular Biophysics

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.4	1.1	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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. In particular, we have studied the structure-activity-relationship of the use-dependent drug, yohimbine. Our studies indicate that the stereo-isomeric configuration of the reactive groups are inconsequential to this use-dependent effect. However, this use-dependent effect is dependent upon the quaternary ammonium at position 4 on the yohimbine molecule. The nitrogen at this site of the active form of yohimbine is positively charged, indicating that a negative site of the receptor is involved in this use-dependent effect.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02316-06 LB

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Comparison of Different Modes of Axonal Stimulation

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
G. Ehrenstein Research Physicist 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	0	0

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This projected has been completed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02317-06-LB

PERIOD COVERED

October 1, 1982 to September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Excitable Membranes and Ion Channels in Cultured Nerve and Muscle Cells

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

H. Lecar Research Physicist LB NINCDS

COOPERATING UNITS *(if any)*

LNP NINCDS, BB NICHD, KE NHLBI

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 *(Use standard unreduced type. Do not exceed the space provided.)*

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. Modification of channel gating by pharmacological agents and neurotransmitters is studied as a means of establishing a picture of synaptic integration based on the properties of membrane ionic channels.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02526-02 LB

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Gated Ionic Channels in Membranes

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

R. E. Taylor Research Physiologist LB NINCDS

COOPERATING UNITS *(if any)*

Dept. of Physiology, UCLA, Los Angeles, CA
Marine Biological Laboratory, Woods Hole, MA

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 *(Use standard unreduced type. Do not exceed the space provided.)*

The study of the effects of initial conditions on sodium and gating currents in the squid axon were completed and a manuscript has been accepted for publication.

The results of measurements of the potassium channel gating currents were analyzed and were presented at the 1983 annual meeting of the Biophysical Society.

The effects of elimination of sodium current inactivation with internal pronase on gating currents and on the fraction of open channels as functions of voltage were examined.

PHS 6040 (Rev. 1/83) GPO 895-100

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02219-08 LB

PERIOD COVERED

October 1, 1982 to September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Structure and function of the perineurium

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

R.E. Taylor Research Physiologist LB NINCDS

COOPERATING UNITS *(if any)*

Laboratory of Neurosciences, NIA

LAB/BRANCH

Laboratory of Biophysics, IRP

SECTION

Section on Molecular Biophysics

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 *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been discontinued.

TAB 10 -- LABORATORY OF CENTRAL NERVOUS SYSTEM STUDIES -- LCNSS/IRP

ANNUAL REPORT

October 1, 1982 through September 30, 1983

Laboratory of Central Nervous System Studies

National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

ANNUAL REPORT
October 1, 1982 through September 30, 1983

Laboratory of Central Nervous System Studies
National Institute of Neurological and Communicative Disorders and Stroke

The major accomplishments of the Laboratory of Central Nervous System Studies over the past year have been as follows:

We continued to define the world-wide problem of human disease caused by the zoonosis of hemorrhagic fever with renal syndrome (HFRS) which we have renamed muroid virus nephropathy. Previously our laboratory demonstrated that HFRS was the most important zoonosis and one of the most important virus diseases of all provinces of China and caused by the same virus as that of Japan, Korea, and Far Eastern Siberian USSR. In the past year we have demonstrated that the Hantaan virus causing the Far Eastern form of HFRS is present in urban rats of most American cities. We have isolated in laboratory rats and tissue cultures and characterized a new virus of the Bunyamwera group of viruses antigenically related to Hantaan virus. We called the new isolate Prospect Hill virus after the Frederick property where we found the type strain in indigenous, wild American rodents. The further clinical, virological and epidemiological elucidation of this world-wide problem and the extension of it to the Americas will occupy dozens of laboratories for the next several decades.

The Prospect Hill virus has yielded a nephropathy model with protein, urea, and nitrogen retention in inoculated chimpanzees and cynomolgus monkeys; many other species of monkeys have been inoculated to determine their susceptability. This is the first nephropathy model of a Hanvirus of the Bunabunyaviridae. Prospect Hill virus has had its three single stranded RNA segments of its genome sequenced at the 3'-OH terminal for 15 to 20 nucleotides. It has thus proved to be a classical member of the Hanvirus group. We have adapted the virus of nephropathica epidemica of Scandinavia to tissue cultures and are passaging it serially in Mongolian gerbils as well as in laboratory-bred Clethyronomys.

In work on kuru, our most significant new contribution has been the clear documentation of incubation periods of thirty years and more in human kuru and the identification of the contaminating episode for several dozen patients occurring in recent years. We discovered that the great majority, in fact over ninety percent of the infants and children of women present at a contaminating event of cannibalism have already come down with kuru. Continued surveillance has revealed no alteration in the pattern of kuru, the disappearance of which emphasizes the artifical man-made nature of the epidemic; kuru virus clearly has no reservoir in nature and no intermediate natural biological cycle for its preservation except in humans.

On Creutzfeldt-Jakob Disease, our continued epidemiological work has made it clear that the one per million per annum incidence and death rate is approximately the same on all six continents in all nations and that high incidence foci are a real phenomenon. We have further demonstrated that in familial cases a single autosomal-dominant gene pattern of occurrence is indeed true in spite of the fact that the disease is caused by a virus. This is the first example in man of an autosomal-dominant single-gene inheritance controlling the appearance of an infectious disease.

The enormous resistance of the unconventional viruses causing kuru and Creutzfeldt-Jakob disease of man and scrapie in animals has resulted in altered procedures in all autopsy rooms, surgical theaters and clinics in the world. Our continued study of the inactivation and the physical properties of these agents is thus manditory in order to set the proper standards for handling possible contamination.

The problem this resistance to inactivation may cause has reached enormous proportions with respect to the hepatitis B vaccine prepared from the hepatitis antigen in serum of human volunteers; some of these volunteers may be incubating the Creutzfeldt-Jakob dementia syndrome. Once this has been suggested, it is apparent that there is no assay procedure sufficient to declare the vaccine safe. Even a chimpanzee assay would require decades and still be uncertain, as shown by our newer work on variation in host range of human strains of Creutzfeldt-Jakob disease.

Our work with primates shows that peripheral routes of inoculation give irregular "takes" and, as expected, are associated with long incubation periods of perhaps one or more decades. We pointed out that an accident with this type of virus actually resulted in tens of thousands of cases of fatal scrapie in British sheep previously free of the disease when a formalinized louping-ill vaccine was contaminated with the scrapie virus. The moral, ethical and legal aspects of continuing to use the hepatitis B vaccine once this problem has been raised and appreciated are enormous.

Determining physical chemical structure of the unconventional viruses using both a mouse-adapted strain of CJD virus and hamster and mouse strains of scrapie virus has been the major target of our laboratory. Recent highly-publicized speculations on the possible very exotic nature of these viruses are based in large degree on our data. Those speculations are ideas we have voiced over many years, but they are all still unprovable. Our own recent data again confirm the absence of any immune response to purified, high-titer virus or any involvement of the immune system in patients with the natural diseases or animals with experimental diseases. We have also been unable to demonstrate a nucleic acid by transfection and annealing (hybridization) techniques. By ultrasonication studies we found the high level of association of the hydrophobic viral particles into aggregates of 1000 monomers or more; this finding invalidates most of the studies in which an extremely small size has been determined by physical means, including equilibrium sedimentation, and also invalidates conventional interpretations of radiation resistance and chemical and enzyme resistances as well. On the other hand, it is clear that a new group of microbes has been defined that challenge the basic tenets of microbiology. Exotic new possibilities suggested by the scrapie virus include abnormal templates for laying down of plasma membranes and neurofilament, small proteins free of nucleic acids which are derepressors of cellular genes responsible for their own synthesis, or the first example of a filamentous virus in mammals. As a major problem for basic medical science, the resolution of this enigma is an inescapable challenge. Our most recent observation of unique helical fibrils in extracts of brains and spleens of animals with scrapie, kuru, and Creutzfeldt-Jakob disease, but not in controls, opens a new and promising possibility that the pathogenic agents themselves have finally been recognized and are a new form of pathogens--"filamentous viruses".

Our epidemiological studies of scrapie in France and elsewhere have revealed that scrapie virus is nearly ubiquitous in butcher shops and restaurants of the world. That it may be responsible for occasional disease in primates has not been epidemiologically established. Yet we now know from our own inoculations that the human viruses of CJD or kuru can cause scrapie in goats, and that goat, sheep and mouse strains of scrapie can cause the Creutzfeldt-Jakob syndrome in several species of monkeys inoculated but not yet in chimpanzees. We have participated in the study of the transmissible scrapie-like agent affecting wild mule deer and moose in Colorado, and in the enormously intriguing demonstration that such infected mule deer develop amyloid plaques in great profusion, as do kuru victims and a portion of the CJD patients.

Our study of the auto-immune antibodies to 10-nm neurofilaments in human patients or experimental animals with kuru, CJD and scrapie, has been extended. Autoantibodies are specifically directed against the 200,000-dalton protein subunit and not to two other components of the 10nm neurofilament. This very specific autoantibody appears in about one-fourth of patients with many other gray matter diseases, as opposed to over one-half of the kuru and CJD patients, and with very much lower incidence in normal control populations or patients with other autoimmune disorders. Thus, much more work on the significance of this enormously specific autoimmune response is now necessary and in progress.

Using monoclonal antibodies developed in this laboratory to various cytoskeletal structures of postnatal and adult hamster brains it has been possible to study the migrations and maturation of neural cells during neurogenesis. We are currently studying in-born errors of metabolism in specific genetic lines of animals with neurological deficits as well as animals born of "slow-virus" infected mothers.

Our work on the high-incidence foci of amyotrophic lateral sclerosis and Parkinson's disease has led to the further confirmation that in these places there is premature aging of the population with early appearance of neurofibrillary tangles in brain. We have now identified the pathogenic mechanism involved in these foci, which has been demonstrated at the epidemiological level to involve early life (in utero ontogenesis, infancy, childhood, adolescence) spent in environments enormously deficient in calcium and magnesium, in "primitive", isolated cultures with no outside food sources and from which the patients have never traveled. With the change in social and economic conditions after World War II in the Japanese Kii peninsula focus and among the Chamorro people on Guam, it is now clear that the calcium and magnesium deficiency no longer pertains and this accounts for the enormous decline in incidences of both diseases. No such decline has occurred in New Guinea, where the focus of both diseases is much more intense, except in one village; people in that village moved away from the region and changed their environmental exposure and economic status and were exposed to imported foodstuffs. This hypothesis is clearly substantiated by environmental analyses of soil, drinking water and foodstuffs. Using neutron-activation analyses and electron probe x-ray microanalysis spectrophotography, it now been demonstrated that hydroxyapatites containing calcium and aluminum and other di- and tri-valent cations are deposited and remain in neurons, particularly in those that develop neurofibrillary tangles. Thus, early parathyroid adjustment required for life in the calcium-deficient environment renders the host vulnerable to heavy metal intoxication with deposition of heavy-metals and calcium in neurons and seems to lead to the premature aging of the brain (the

appearance of neurofibrillary tangles), and degenerative disease syndromes of the CNS. The implications of these discoveries for the study of motor-neuron diseases, parkinsonism-dementia and of the aging process itself are enormous and have already influenced research.

Our collaborative work on the use of viral nucleic-acid probes for demonstrating by in situ hybridization the presence of genomic copies of viruses in neurons has led to an extremely important discovery. By In situ hybridization, copies of viral genomes were identified in neurons of control subjects, rather than in Guamanian ALS and PD and American ALS brain specimens. This finding casts a shadow over that whole methodological approach to all virology of chronic human diseases.

Our studies on the introduction of cysticercosis into previously virgin populations of Papua New Guinea and West New Guinea demonstrated a self-limited form of grand mal epilepsy in older children and adults, which is undoubtedly caused by the larval migrans phase of pig tapeworm infestation at a period before real cysts have developed in the brain. This self-limited disease requires no antiepilentic therapy, and the patients are left with no further seizures and no other obvious sequelae. We are now following the situation to determine which patients will later develop calcified intracerebral cysts, breakdown of cysts, and intractible epilepsy or other brain syndromes requiring neurosurgical treatment or elaborate anticysticercus chemotherapy. We have developed a sensitive ELISA test, now in worldwide use, for studying cysticercosis in man and animals, and have recently improved this by the anlysis of the antigens involved and the preparation of purer antigens. We have demonstrated in Southeast Asian epilepsy clinics, in areas like Bali where cysticercosis is highly prevalent, that this newly-appreciated diagnosis is probably the cause of much of the self-limited new epilepsy seen.

Our work on male pseudohermaphroditism in a focus among the Anga people in the New Guinea highlands has established that the syndrome is similar to that in the Dominican Republic, resulting from hereditary deficiency of delta-H steroid reductase, which prevents the production of dihydrotestosterone.

Our associated study of psychosexual development in this New Guinea population of pseudohermaphrodites and of adjacent populations has influenced basic thinking on gender and role identification in man, and of the biological and psychological effects of diverse cultural patterns of psychosexual development. Patterns of permissive and promiscuous prepubertal heterosexuality, of similarily promiscuous and early homosexuality, and of total sexual abstinance in different adjacent cultures provide important natural laboratories for study of child development that have great impact on psychiatric thinking.

Physiological and growth and development studies in these isolated cultures over 30 years have revealed incredible patterns of premature aging in some populations and of enormous delay in puberty and menarche in others. Migration and sudden cultural change has resulted, in these latter groups in enormous advance in the age of puberty and acceleration of the adolescent growth spurt. Thus, these situations now provide a fruitful source of study of factors related to the control of the age of puberty, one of the most important problems facing modern society.

Acquired immune deficiency syndrome has been under investigation for several years as a continuation of Dr. Gajdusek's investigations of a similar "AIDS" epidemic of interstitial plasma cell pneumonia in infants in Europe in the 1940s, '50s, and '60s which resulted in the first paper in English on P. carinii. Both P. carinii and cytomegalic inclusion disease were causes of death; the epidemic receded without the primary cause of the immune deficiency having been identified. In the current outbreak in the U.S., chronic encephalitis has been brought to our attention in the past two years. We have inoculated tissue from AIDS (and Kaposi's sarcoma) patients into many animals, including juvenile chimpanzees and monkeys, which are under long-term immunological surveillance. Tissue cultures and explanted tissues from AIDS victims are cocultivated in an attempt to grow a virus provoking primary immune deficiency. We are using our usual techniques to search for inapparent infections of the cultures. Pre-AIDS tissue specimens (i.e. gay lymphadenopathy syndrome) and specimens from controls in contact with AIDS patients have been inoculated into many species of subhuman primates and apes. Some of the pre-AIDS donors have subsequently developed AIDS.

We are also investigating the two most interesting viruses isolated from AIDS patients which are candidates for its cause--the human T-cell leukemia virus (Gallo et al.) and the French retrovirus of Montaigner--in inoculated primates, including newborn and in utero animals. The eight cases of AIDS of infants and small children in Newark, New Jersey have developed a concomitant encephalopathy which is under investigation using brain biopsy and early autopsy. We are concentrating our efforts on contacts of AIDS patients who have developed immune deficiency and chronic lymphadenopathy before opportunistic investigations have intervened.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 01282-19 CNSS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)

Neurobiology of Population Isolates: Study of Child Growth and Development, Behavior and Learning, and Disease Patterns in Primitive Cultures.

PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages.)

(Name, title, laboratory, and institute affiliation)

D.C. Gajdusek, M.D., Chief, Laboratory of Central Nervous System Studies, NINCD

COOPERATING UNITS (if any)

AUSTRALIA: Dr. Timothy Asch, Australian National University, Canberra; Dr. Cyril Curtain, CSIRO, South Melbourne; Dr. Eric French, Mt. Eliza: Dr. Chev Kidson, Queensland Institute of Medical Research, Brisbane; (continued)

LAB/BRANCH

Laboratory of Central Nervous System Studies, Intramural Research Program

SECTION

INSTITUTE AND LOCATION

NINCDS, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
12	8	4

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☒ (a2) Interviews

SUMMARY OF WORK (Use standard unreduced type. Do not exceed the space provided.)

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. Oportunistic investigation of problems phrased by man in isolation is the basis of approach from which all our studies have evolved. Techniques of molecular biology, immunology, virology, and biochemistry on specimens and field epidemiological, clinical, linquistic, and behavioral studies in cultural isolates and genetic and/or geographically isolated primitive bands yield more easily interpretable data than in cosmopolitan societies. Data and specimens collected on expeditions to Micronesia, Polynesia, Solomon Islands, New Hebrides, New Guinea, Indonesia, South 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), culturally modified sexual behavior and different syste4ms and patterns of symbolization in dance, music and other arts 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, spastic paraparesis, familial parkinsonism, other CNS degenerations, hysterical disorders, schizophrenia, suicide, neoplasms, goiter, cretinism, rheumatoid diseases, diabetes, asthma, chronic lung disease, malaria, filariasis, leprosy, cysticercosis, and other infections are investigated. Zoonoses such as hemorrhagic fever with renal syndrome in China, Japan, Korea, USSR, Scandinavia, and the Balkans are studied including these newly recognized Bunyamwera viruses in the U.S. Acquired immune deficiency syndrome studied by our group in 1950-1960 have been reinitiated. Patterns of very delayed puberty and menarche and premature aging in certain groups are studied and factors that control age of puberty and senescence are under investigation. Human evolution and adaptability to high altitude, excessively wet or arid climes, variable food supply, mineral deficiencies, toxic exposures and responses to severe diseases or social/psychological stress are under investigation in appropriate population isolates.

OTHERS: Michael Alpers, M.D.; Judith Farquhar, M.A.; Peter Fetchko, M.A.; Dmitry Goldgaber; Klaus Mannweiler, M.D.;. Steven Ono, M.S.; Robert G. Rohwer, Ph.D.; Donald Rubinstein, Ph.D.; Vincent Zigas, M.D.; Francoise Cathala, M.D.; Kwang-Ming Chen, M.D.; Olivia Cruz, M.D.; Richard Feinberg, Ph.D.; Robert MacLennan, M.D.; Father David Gallus; Fusahiro Ikuta, M.D.; Jesus Raglmar; John Runman, Marie-Claude Dubois, Ph.D., Millicent Coker-Vann, Ph.D., Mario Barragan, M.D., Sina Bahmanyar, M.D., Andres Salazar, M.D., Chen-ting Chen, M.D.

COOPERATING UNITS: continued

Dr. L. Herzberg, Perth Medical Center, Nedlands; Dr. Robert L. Kirk, Australian National University, Canberra; Dr. Robert MacLennan, University of Sidney, Sidney; Dr. Colin Masters, University of Perth, Perth; Dr. John Sheridan, Queensland Institute of Medical Research, Herston; Dr. Fiona Stanley, Perth Medical Center, Nedlands; Dr. Neville Stanley, University of Western Australia, Nedlands; Dr. Stephen Wurm, Australian National University, Canberra, Dr. Euan Scrimgeour, Mt. Lawley; Dr. J. Hargrave, Darwin.

BOLIVIA: Dr. Mario Barragan, La Paz; Dr. Mario Michael Zamora, Department of Neurologic y Neurocirugia, La Paz.

BRAZIL: Prof. Helio L. de Oliveira, Universidade de Sao Paulo, San Paulo.

CANADA: Dr. Kenneth Dresser, Toronto; Dr. Jack Hildes, University of Manitoba, Winnipeg; Dr. Otto Schaefer, National Health and Welfare, Edmonston.

CHINA: Dr. H.E. Ge, Hubei Province Medical School, Wuchang; Dr. Chin-min Hsiang, Virus Research Institute, Hupeh Medical College; Dr. Hung Toa, Department of of Electron Microscopy, Peking University, Peking; Dr. Zhi-Yi Xu, Department of Epidemiology, Shanghai 1st Medical College, Shanghai; Dr. Zheng, Virus Research Institute, Hubei Medical College, Hubei.

COLOMBIA: Dr. R. Barrett, Cali; Dr. R. Bijo, Hospital San Andres, Tumaco; Dr. Alvaro Duenas, Department of Microbiology, University del Valle, Cali; Dr. H. Groote, National Institutes of Health, Bogota; Dr. G. San Martin, National Institutes of Health, Bogota; Dr. G. Toro, National Institutes of Health, Bogota; Dr. V. Zaninovic, Neurologic Clinic University Hospital, Cali.

ENGLAND: Mrs. Elisabeth Beck, Institute of Psychiatry, London; Dr. M.C. Clarke, Agricultural Research Council, Compton; Prof. P.M. Daniel, Royal College of Surgeons, London; Dr. A.J. Duggan, Wellcome Museum of Medical Science, London; Dr. George Nurse, London.

FIJI: Mr. Ron Crocombe, University of South Pacific, Suva.

FINLAND: Dr. Juhani Lahdevirta, University of Finland, Helsinki.

FRANCE: Prof. Jacques Bert, Centre Hopital et Universite, Marseille; Dr. Francoise Cathala, Hopital de la Salpetriere, Paris; Dr. Maurice Godelier, L'Ecole Pratique Des Hautes Etudes, Paris; Dr. Jean Guiart, Paris.

COOPERATING UNITS: continued

GERMANY: Dr. Freidrich Deinhardt, Max-van-Petteenkoffer Institute, Munich; Dr. Klaus Mannweiler, Henrich-Pette-Institute fur Virologie und Immunologie, Hamburg; Dr. Wulf Schiefenhovel, Max-Planck Institut fur Verhaltensphysiologie, Percha; Dr. Heinz Stephan, Max-Plank-Inst. fur Hirnforschung, Frankfurt-am-Niederrad.

INDONESIA: Father David Gallus, Misi Katolik, Jayapura; Dr. Surjadi Gunawan, Public Health Department, Jakarta; Dr. B.A. Kawengian, Dr. Soewahjudi, Public Health Department, Jakarta; Bishop Alphonse Sowada, Catholic Mission, Jayapura; Dr. Budi Subianto, Public Health Department, Jayapura, Dr. Julie Sulianti Saroso, Public Health Department, Jakarta; Father Frank Trenkenkshuh, Catholic Mission Asmat, Jayapura; Dr. Laode R. Tumade, Department of Public Health, Jayapura; Mr. Jeff Verstegen, Associated Mission Aviation, Jayapura; Dr. W. Vriend, Wamena General Hospital, Wamena, Irian Jaya.

ITALY: Marek and Allison Jablanko, Perugia.

KENYA; Dr. Leendert C. Vogel, University of Nairobi, Nairobi.

MEXICO: Dr. Julio Sotelo, Institut Nacional de Neurologie, Mexico City; Dr. Reinhart Ruge, Cernavaca.

NETHERLANDS: Father Ben van Oers, Missiehuis, Tilburg; Dr. Jaap Goudsmit, University of Amsterdam, Dr. Fransje van der Waals, Amsterdam.

NEW HEBRIDES: Capt. John Barley, Treasury/Customs Department, Port Vila; Dr. Kirk Huffman, Cultural Centre, Port Vila; Dr. Ravi Ramdoyal, World Health Organization, Port Vila; Dr. Ratard, French Hospital, Port Vila.

NEW ZEALAND: Dr. R.W. Hornabrook, Wadestown; Dr. J. M. McKenzie, University of Otago, Dunedin; Dr. J. A. R. Miles, Otago; Dr. Alistair G.C. Renwick, University of Auckland, Auckland.

PAPUA NEW GUINEA: Dr. Michael Alpers, Institute of Medical Research, Goroka; Dr. H.A. Brown, Port Moresby; Rev. F. Fischer, Lutheran Mission, Okapa; Dr. J. Linsley Gressitt, Wau Ecology Institute, Wau; Richard Lloyd, Summer Institute of Linguistics, Aiyura; Mr. Ivan Mbagintao, J.K. McCarthy Museum, Goroka, Dr. Stuart Merriam, Highland Christian Mission, Yagusa; Dr. Jack Onno, Department of Public Health, Port Moresby; Dr. Kerry Pataki-Schweizer, University of Papua New Guinea, Port Moresby; Euan Scrimgeour, University of Papua New Guinea; Dr. Alan Tarutia, Public Health Headquarters, Konedobu; Dr. Jeffrey Tuvi, Boroko.

PERU: Dr. Carlos Monge, Universidad Cayetano Heredia, Lima.

PHILIPPINES: Dr. Benjamin Catubay, Provincial Health Office, Ilocos Norte; Dr. Martesio C. Perez, University of Philippines, Manila; Dr. Virginia Basaca Sevilla, Ministry of Health, Manila; Dr. Elizabeth Zarasoe-Yoo, University of Philippines.

MADAGASCAR: Dr. Pierre Coulanges, Institute Pasteur de Madagascar, Antanarivo.

MAURITIUS: Dr. B. Gurburrum, Ministry of Health, Port Louis.

REPUBLIC OF CHINA: Dr. R. Palmer Beasley, University of Washington, Taipei.

REUNION ISLAND: Dr. Charles Bosquet, Hopital de Terre Rouge, St. Pierre; Dr. Jean-Baptiste Dandelot, Hopital de Terre Rouge, St. Pierre; Dr. Maurice Jay, Hopital Psychiatrique, St. Paul.

SCOTLAND: Dr. Alan G. Dickinson, A.R.C. Animal Breeding Research Organization, Edinburgh; Dr. J. D. Macgregor, Shetland Health Board, Shetland.

SINGAPORE: Chong Keat Lim, Architects Team 3; Prof. Dr. Lim Kok Ann; Dr. Ivan Polunin, University of Singapore; Dr. Foo Keong Tatt, Singapore General Hospital.

SOLOMON ISLANDS: Dr. D. Mackay, Center Hospital, Honiara; Dr. A.M.O. Solomon, Health Department; Kirakira; Dr. B. Wilkin, Central Hospital, Honiara.

SWITZERLAND: Dr. Liana Bolis, World Health Organization, Geneva; Dr. Stephen Fazekas, Basel Institute for Immunology, Basel.

USSR: Dr. Mikhail Petrovich Chumakov, Institute for Poliomyelitis and Virus Encephalides, Moscow; Dr. Lydia L. Fadeeva, Ulitsa Valters Ulbrichta, Moscow; Dr. L.G. Goldfarb, Institute of Poliomyelitis and Viral Encephalitides, Moscow; Prof. Vera I. Il'yenko, All-union Research Institute of Influenza, Leningrad; Prof. D.K. Lvov, D.I. Ivanovskii Institute of Virology, Moscow; Dr. Prokopii Andrevich Petrov, Iakut Ministry of Public Health, Iakutsk; Dr. Anatoli Alexandrovich Smordintsev, Leningrad; Dr. A.I. Vladimyrtsev, Iakutsk Ministry of Health, Iakutsk; Dr. Victor Zhadanov, Ivanovskii Institute of Virology, Moscow.

UNITED STATES: Alabama: Dr. James Dutt, University of South Alabama, Mobile; Dr. Charles Hoff, University of South Alabama, Mobile; Dr. Wladimir Wertelecki, University of South Alabama, Mobile. Arizona: Dr. Tim Kuberski, National Institute of Arthritis, Metabolism, and Digestive Diseases, Phoenix. California: Mr. James Boykin, Valencia; Dr. L.L. Cavalli-Sforza, Stanford University, Palo Alto; Dr. Michael N. Oxman; V.A. Hospital, San Diego. Delaware: Dr. Roger Rodrique, Wilmington. Hawaii: Dr. Arwin Diwan, University of Hawaii, Honolulu, Dr. Leon Rosen, Pacific Research Center, Honolulu; Don Rubinstein, University of Hawaii, Honolulu; Dr. Gordon Wallace, Pacific Research Station. Illinois: Judith Farquhar, Chicago; Dr. Walter R. Kirschbaum, Chicago. Maryland: Dr. Richard T. Johnson, Johns Hopkins Hospital, Baltimore; Dr. David Lang, University of Maryland, Baltimore; Dr. Guy McKhann, Johns Hopkins University, Baltimore; Dr. Chris Plato, Gerontology Research Center, Baltimore; Dr. Constantine Sakles, University Hospital, 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. Masschusetts: Dr. John Enders, Brookline; Mr. Peter Fetchko, Peabody Museum,

COOPERATING UNITS: continued

UNITED STATES: (continued)
Salem. Michigan: Prof. J.V. Neel, Univeristy of Michigan, Ann Arbor; Dr. Ernst A. Rodin, Lafayette Clinic, Detroit. Minnesota: Dr. Leonard Kurland, Mayo Clinic, Rochester; Dr. G. Albin Matson, Minneapolis. Nevada: Dr. Warren V. Huber, V.A. Medical Center, Reno. New Jersey: Dr. Karl Maramorosch, Rutgers University, New Brunswick; Dr. Richard Masland, Englewood. New York: Dr. Robert Glasse, Queen's College, Flushing; Dr. Shirley Lindenbaum, The New School, New York; Dr. Ralph D. Peterson, New York Hospital-Cornell Medical Center, New York; Dr. Roger D. Traub, IBM Thomas W. Watson, Yorktown. Ohio: Dr. Richard Feinberg, Kent State University, Kent; Dr. Frank P. Saul, Medical College, Toledo; Dr. Arthur G. Steinberg, Case Western Reserve University. Pennsylvania: Dr. Paul T. Baker, Pennsylvania State University, University Park; Dr. Napolean Chagnon, Pennsylvania State University, University Park; Drs. Werner and Gertrude Henle, Children's Hospital of Philadelphia, Philadelphia. Rhode Island: Dr. Terrence E. Hays, Rhode Island College, Providence;. Dr. John Strom, Rhode Island Hospital, Providence. South Carolina: Dr. Paul M. Hoffman, V.A. Hospital, Charleston; Dr. Albert Sabin, Medical University of South Carolina, Charleston. Texas: Dr. Heather D. Mayor, Baylor University Medical School, Houston; Dr. Steven Wiesenfeld, Southwest Allergy Service, Inc., Midland. Washington: Dr. Ronald DiGiacomo, University of Washington, Seattle. Wisconsin: Dr. G.R. Hartsough, Great Lakes Mink Association, Pittsville; Dr. Richard F. Marsh, University of Wisconson, Madison; Dr. Gabriel Zu Rhein, University of Wisconsin, Madison.

YUGOSLAVIA: Dr. A. Terzin, Dept. of Microbiology, Faculty of Medicine, Zagreb; Prof. J. Veseniak-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 and isolated populations of Asia, Africa, Australia, Indonesia, Melanesia, Micronesia, Polynesia, South and Central America and the Arctic.

Sub-Project IX: Experimental developmental neuropediatrics in infantile programming: an empirical approach to the language of information input into the nervous system.

Sub-Project X: Ciphers and notations for the coding of sensory and motor data 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 in primitive or geographically, genetically, culturally, or socially isolated groups. Includes studies such as:

1. Clinical variations of ALS and PD on Guam and in West New Guinea.
2. Non-Chamorro ALS and PD on Guam.
3. Genetic Studies on Normal Chamorro and ALS-PD patients.
4. Search for trace metals in the CNS of ALS-PD patients.
5. Patterns of osteoporesis, osteoarthritis, and bone deformities among normal Chamorro and ALS-PD patients.
6. Attempts to transmit ALS-PD to nonhuman primate hosts.
7. Pharmacological studies on PD.
8. Epidemiological surveillance of ALS and PD in the Northern Mariana Islands.
9. Trace metals in the environment in high incidence motor neuron disease foci of Guam, Irian Jaya, West New Guinea, and Australia.
10. Study of Pacific spastic paraparesis in Colombia.
11. Study of Viliuisk encephalomyelitis in Yakut people of Siberia.

Sub-Project XIII: Studies of high incidence of non-neurological disease in specific racial and ethnic groups and in primitive, or geographically genetically, culturally, or socially isolated groups. Includes studies such as:

1. Asthma in high incidence in isolated Oceanic populations.
2. Congenital Still's disease
3. AIDS in its relationship to Kaposi's sarcoma of the tropics.
4. AIDS and its relationship to the 30 year epidemic of interstitial plasma cell pneumonia in infants across Europe in the 1930's thru 1950s.

Project Description: Neurobiology of Population Isolates: Study of Child Growth and Development, Behavior and Learning, and Disease Patterns in Primitive Cultures (described fully on pages 1-LCNSS/IRP through 5-LCNSS/IRP.

Publications: Listed on pages 20-LCNSS/IRP through 32-LCNSS/IRP.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 00969-19 CNSS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Chronic CNS Disease Studies: Slow, Latent and Temperate Virus Infections

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

D.C. Gajdusek, M.D., Chief, Laboratory of Central Nervous System Studies, NINCDS

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, IRP, NINCDS

SECTION

INSTITUTE AND LOCATION

NINCDS, 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 *(Use standard unreduced type. Do not exceed the space provided.)*

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 dentias, spinocerebellar ataxias, epilepsy, chronic encephalitis with focal epilepsy, muscular dystrophies, chronic schizophrenia, autism, SSPE, PML, dialysis encephalopathy, and intracranial neoplasm. 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 diseased or infectious brain. 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.

Familial and nonfamilial dementia and the dementias of senility are studied. The autoimmune responses to specific brain antigens in CNS diseases and are under intensive investigation. DNA in situ hybridization and electrophoretic focusing partition of proteins along with enzymatic and hybridoma immunofluorescence and many other techniques are used to try to identify viral subunits and partial genomes in tissues in chronic diseases.

PRINCIPLE INVESTIGATORS: 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.; Paul W. Brown, M.D.; Chen-ting Chin, M.D.; Marie-Claude Moreau-Dubois, Ph.D.; Ryo Fukatsu, M.D.; Ralph M. Garruto, Ph.D.; C.M. Hsiang, M.D.; Yasuo Kuroda, Ph.D.; Pyung-Woo Lee, Ph.D.; Maryellen F. Masciangelo, Ph.D.; Carlo Masullo, M.D.; T. Nakamura, M.D.; Maurizio Pocchiari, M.D.; Pamela Rodgers-Johnson, M.D.; Robert G. Rohwer, Ph.D.; Akira Takenaka, M.D.; Richard T. Yanagihara, M.D.; Francoise Cathala, M.D., Dimitry Goldgaber, Ph.D.;

COOPERATING UNITS: (continued)

AUSTRALIA: Dr. Colin Masters, University of Western Australia, Perth; Dr. Eric Shaw, Red Cross Blood Transfusion Service, Brisbane; Dr. Margaret Sabine, University of Sydney, Sydney.

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. Newcastle, 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, Kaohsiung Medical College, Kaohsiung.

COLOMBIA: Dr. V. Zaninovic, Neurological Clinic, University Hospital, Cali; Dr. Alvaro Duenas, Department of Microbiology, University del Valle, Cali.

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.

COOPERATING UNITS: (continued)

FINLAND: Prof. Nils Oker-Blom, University of Helsinki, Helsinki.

FRANCE: Dr. Jacques Bert, Centre Hopital et Universite, Marseille; Dr. Francoise Cathala, Hopital de la Salpetriere, Paris; Dr. Henri-Pierre Cathala, Hopital 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, Hopital de La Timone, Marseille.

GERMANY: Dr. Freidrich Deinhardt, Max-van-Pettekoffer Institute, Munich; Dr. Klaus Mannweiler, Henrich-Pette-Institute fur Virologie und Immunologie, Hamburg; Dr. W.K. Muller, Country Psychiatric Hospital, Wiesloch; Dr. Volker ter Meulen, Institute fur Virologie, Wurzburg; Dr. Wolfgang Zeman, Lahstein.

GUAM: Dr. Kwang-Ming Chen, NINCDS Research Center, Tamuning; Dr. Leon Concepcion, Guam Memorial Hospital, Agana; Dr. Olivia Cruz, NINCDS Research Center, Tamuning; Jose Torres, NINCDS Research Center, Tamuning; Dr. Yushiro Uehavashi, NINCDS Research Center, Tamuning; Dr. Richard T. Yanagihara, NINCDS Research Center, Tamuning.

ICELAND: Dr. Margret Gudnadottir, University of Iceland, Reykjavik; Dr. P.A. Palsson, University of Iceland, Reykjavik; Dr. G. Petursson, University of Iceland, Reykjavik.

INDONESIA: Dr. Budi Subianto, Public Health Department, Jayapura.

JAPAN: Dr. Tomonobu Aoki, Department of Microbiology, Kyushu University, Fukuoka; Dr. Fushahiro Ikuta, Brain Research Institute, Niigata; Dr. Kiyotaro Kondo, Brain Research Institute, Niigata; Dr. Reisaku Kono, National Institute of Health, Tokyo; Dr. Yoshigoro Kuroiwa, Kyushu University, Fukuoka; Dr. Takao Makifuchi, Brain Research Institute, Niigata; Dr. Ryoichi Mori, Kyushu University, Fukuoka; Dr. Shigeru Mori, Brain Research Institute, Niigata; Dr. Nobuyuki Murakami, Nagoya University of School of Medicine, Nagoya; Dr. Seiho Nagafuchi, Kyushu University, Fukuoka; Dr. Ikuya Nagata, Nagoya University, Nagoya; Dr. Hiroshi Oda, Kagoshima University, Kagoshima; Dr. Tadao Tsubaki, Tokyo Metropolitan Neurological Hospital, Tokyo; Dr. Yoshiro Yase, Wakayama Medical College, Wakayamashi.

KOREA: Dr. Ho Wang Lee, Korea University Medical College, Seoul.

MEXICO: Dr. Julio Sotelo, Institut Nacional de Neurologia, Mexico City.

NETHERLANDS: Dr. Jan ten Brink, University Hospital of Amsterdam, Amsterdam; Dr. Jan van der Noordaa, Laboratorium voor GezondheidsLeer, Amsterdam.

NEW ZEALAND: Dr. P. W. Hornabrook, Wadestown.

COOPERATING UNITS: (continued)

PAPUA NEW GUINEA: Dr. Michael Alpers, Institute for Medical Research, Goroka.

PERU: Dr. Luis Palomino, Hospital Santo Toribio, Lima.

POLAND: Dr. P.P. Liberski, Department of Neurology, Lodz; Prof. Dr. Ewa Osetowska, Polish Academy of Sciences, Minsk.

PUERTO RICO: Dr. Victor Mojica, Veterans Administration Center, San Juan.

REPUBLIC OF CHINA: Prof. Chi-lu Chen, National Taiwan University, Taipei; Dr. C.H. Yen, National Health Administration; Taipei; Dr. Chin-Yun Yii, Kaohsiung Medical College, Kaohsiung.

SCOTLAND: Dr. Alan G. Dickinson, A.R.C. Animal Breeding Research Organization, Edinburgh; Dr. Hugh Fraser, A.R.C. Animal Breeding Research Organization, Edinburgh; Dr. J.D. MacGregor, Shetland Health Board, Shetland.

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.

SWITZERLAND: Dr. Christoph Bernoulli, Universitsspital, Zurich; Dr. Liana Rolis, World Health Organization, Geneva; Dr. Breget, University of Geneva, Geneva; Dr. B. Ney, University of Geneva, Geneva.

USSR: Dr. Mikhasil Petrovich Chumakov, Institute of Poliomyelitis and Virus Encephalides, Moscow; Dr. Lydia L. Fadeeva, Ulitsa Valtera Ulbrichta, Moscow; Dr. Sophia Janovna Gaidamovich, Ivanovskii Institute of Virology, Moscow; Prof. Vera I. Il'yenko, All-union Research Institute of Influenza, Leningrad; Dr. Prokopii Andrevich Petrov, Iakut Ministry of Public Health, Iakutsk; Dr. Vanda V. Pogodina, The Institute of Poliomyelitis and Virus Encephalitides, Moscow; Dr. Peter Rytik, Bilorussioan Institute of Epidemiology, Minsk.

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,

COOPERATING UNITS: (continued)

UNITED STATES: (contined)
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 Poos, 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 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 Hosoital 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. 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

UNITED STATES: (continued)
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. A. Gligic, Institute of Immunology and Virology, Beograd; Dr. Miha Likar, Mikrobioloski Institut, Ljubljana; Dr. D. Terzin, Institute of Virology, Serajevo; 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 sub acute 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 encephlopathies.

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 chraacterization of associated virus.

Sub-Project XIV: Electron microscopic membrane studies of subactue spongiform virus encephalopathies.

Sub-Project XV: Characterization and identification of new herpes viruses from explant cultures of tissues from subhuman promates.

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 subhuman 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 mitrochrondrial 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 immunadsorbent (ELISA) test for the diagnosis and epidemiology of cystercercosis-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 spoingiform viruses on nerve cells grown in vitro.

Sub-Project XXXVI: In vivo and in vitro studies to determine the etiology of myasthenia gravis, Viliuisk encephalomyelitis and ALS-PD in high incidence foci of the Western Pacific.

Sub-Project XXXVII: Neurophysiological study of animals experimentally infected with subacute spongiform virus encephalopathies.

Sub-Project XXXVIII: Studies on in vivo pathogenecity of the retroviruses related to AIDS: HTLV (Gallo); French LAV and LD15GAO virus (Montagnier).

Sub-Project XXXIX: Attempts to transmit or isolate in vitro an etiological agent from AIDS, from pre-AIDS patients with lymphadenopathy syndrome, and from encephalitis associated with AIDS.

Project Description: Chronic Central Nervous System Disease Studies (described fully on pages 1-LCNSS/IRP through 5-LCNSS/IRP).

The projects (I through XXXIX) 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. 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: Pages 20-LCNSS/IRP through 32-LCNSS/IRP

1. Amyx, H.L., Asher, D.M., Gibbs, C.J., Jr. and Gajdusek, D.C.: Future needs of primates in exotic diseases. In Kalter, S.S. (Ed.): Viral and Immunological Diseases in Non-human Primates. Alan R. Liss, New York, 1983, pp. 31-37.

2. Amyx, H.L., Gibbs, C.J., Jr. and Gajdusek, D.C.: Experimental Creutzfeldt-Jakob disease in cats. In Court, L. and Cathala, F. (Eds.): Virus non conventionnels et affections du système nerveux central. Masson, Paris, 1983, pp. 358-362.

3. Amyx, H.L., Salazar, A.M., Newsome, D.A., Gibbs, C.J., Jr. and Gajdusek, D.C.: Nasopharyngeal carcinoma with intracranial extension in a chimpanzee. Journal of the American Veterinary Medical Association 181:11 (December 1), 1425-1426, 1982.

4. Aoki, T., Gibbs, C.J., Jr., Sotelo, J. and Gajdusek, D.C.: Heterogenic autoantibody against neurofilament protein in the sera of animals with experimental kuru and Creutzfeldt-Jakob disease and natural scrapie infection. Infection and Immunity 38:1 (October), 316-324, 1982.

5. Blake, N.M., Kirk, R.L., Wilson, S.R., Garruto, R.M., Gajdusek, D.C., Gibbs, C.J., Jr. and Hoffman, P.: Search for a red cell enzyme or serum protein marker in amyotrophic lateral sclerosis and parkinsonism-dementia of Guam. American Journal of Medical Genetics 14:? (February), 299-305, 1983.

6. Brody, J. and Gibbs, C.J., Jr.: Chronic neurological diseases. Subacute sclerosing panencephalitis, progressive multifocal leucoencephalitis, kuru and Creutzfeldt-Jakob disease. In Evans, A.S. (Ed.): Viral Infections of Man, Epidemiology and Control, Chapter 27. Second edition, A.S. Evans, editor. Plenum, New York, 1982, pp. 675-696.

7. Brown, P., Cathala, F. and Sadowsky, D.: Correlation between population density and the frequency of Creutzfeldt-Jakob disease in France. Journal of the Neurological Sciences 60, 169-176, 1983.

8. Brown, P., Rohwer, R.G., Amyx, H.L., Gibbs, C.J., Jr. and Gajdusek, D.C.: Laboratory and hospital disinfection of spongiform encephalopathy viruses. In Court, L. and Cathala, F. (Eds): Virus non conventionnels et affections du système nerveux central. Masson, Paris, 1983, pp. 509-517.

9. Brown, P., Rohwer, R.G., Green, E.M. and Gajdusek, D.C.: The effect of chemicals, heat, and histopathologic processing on high-infectivity hamster-adapted scrapie virus. In Court, L. and Cathala, F. (Eds): Virus non conventionnels et affections du système nerveux central. Masson, Paris, 1983, pp. 156-163.

10. Brown, P., Salazar, A.M., Gibbs, C.J., Jr. and Gajdusek, D.C.: Alzheimer disease and transmissible viral dementia (CJD). In Sinex, F.M. and Merril, C.R. (Eds.): Alzheimer's disease, Down's Syndrome, and Aging. Annals of the New York Academy of Sciences, 396, 131-143, 1982.

11. Cathala, F., Lecanuet, P. and Brown, P.: La maladie de Creutzfeldt-Jakob en France. In Colloque sur Virus Lents et Infections Virales Lentes, Paris, June 2, 1983, p. 17.

12. Chen, K.-M., Makifuchi, T., Garruto, R.M. and Gajdusek, D.C.: Parkinsonism-dementia in a Filipino migrant: a clinicopathologic case report. Neurology 32:11 (November), 1221-1226, 1982.

13. Court, L., Breton, P., Bassant, M.-H., Gourmelon, P., Dormont, D., Mestries, J.-C., Cathala, F., Gibbs, C.J., Jr. and Gajdusek, D.C.: La maladie de Creutzfeldt-Jakob experimental du singe ecureuil: aspect clinique et electroencephalographique. Abstract No. 110 in Travaux Scientifiques des Chercheurs du Service de Sante des Armees, No. 3. Direction Centrale du Service de Sante des Armees, Clamart, France, 1982, p. 318.

14. Diwan, A.R., Lee, H.-W., Yanagihara, R., Lee, P.-W., Leduc, M.R., Bomgaars, M.R., Halstead, S.B., Johnson, K.M., Gibbs, C.J., Jr. and Gajdusek, D.C.: Prevalence of antibodies to Hantaan or closely related virus amongst rodents and humans in the state of Hawaii. Abstract No. 89 in Abstracts of the First International Symposium on Public Health in Asia and the Pacific Basin, Honolulu, March 7-11, 1983. no pp.

15. Fieschi, C., Orzi, F., Pocchiari, M., Nardini, M., Rocchi, F., Asher, D.M., Gibbs, C.J., Jr. and Gajdusek, D.C.: Creutzfeldt-Jakob disease in the province of Siena: two cases transmitted to monkeys. Italian Journal of Neurological Sciences 1, 61-64, 1983.

16. Franko, M.C., Gibbs, C.J., Jr., Lee, P.-W. and Gajdusek, D.C.: Monoclonal antibodies to Hantaan virus. Abstract No. 93 in Abstracts of the First International Symposium on Public Health in Asia and the Pacific Basin, Honolulu, March 7-11, 1983. no pp.

17. Franko, M.C., Gibbs, C.J., Jr., Lee, P.-W. and Gajdusek, D.C.: Monoclonal antibodies specific for Hantaan virus. Proceedings of the National Academy of Sciences USA 80: (July), 4149-4153, 1983.

18. Gajdusek, D.C.: Muroid virus nephropathies and muroid viruses of the Hantaan virus group. In Proceedings of the Eighth International Congress of Infectious and Parasitic Diseases, Stockholm, June 7-11. Scandinavian Journal of Infectious Diseases, Suppl. 36, 1982, 96-108.

19. Gajdusek, D.C.: Dementia and the aging nervous system: Causes and suspected etiologies as a result of natural experiments in isolated human groups. Abstract in Abstractd of the Fifty-second Annual Meeting of the American Association of Physical Anthropologists, Indianapolis, April 7- American Journal of Physical Anthropology 60:2 (February), 194-195, 1983.

20. Gajdusek, D.C.: In Memoriam. Vincent Ziqas. 1920-1983. Neurology 33:9 (September), 1199-1200, 1983.

21. Gajdusek, D.C. and Gibbs, C.J., Jr.: Slow infection of the CNS with unconventional viruses and attempts to demonstrate a slow-virus aetiology in amyotrophic lateral sclerosis and parkinsonism dementia. In Refsum, S., Bolis, C.L., and Sanchez, A.P. (Eds): Proceedings of the International Conference on Peripheral Neuropathies, Madrid, June 24-25, 1982, pp. 93-110.

22. Gajdusek, D.C. and Gibbs, C.J., Jr.: Infeccion lenta del SNC por virus no convencionales, e intentos de demonstrar una etiologia virica lenta en la esclerosis lateral amiotrofica y en el sindrome Parkinson-Demencia. In Refsum, S., Bolis, C.L., and Sanchez, A.P. (Eds): Proceedings of the WHO International Conference on Peripheral Neuropathology, Madrid, June 24-25, 1982, pp. 31-50.

23. Gajdusek, D.C., Gibbs, C.J., Jr., Lee, P.W., Svedmyr, A., Amyx, H.L. and Goldgaber, D.: Global epidemiology of Hantaan and related viruses. In: Abstracts of the International Conference on Comparative Virology, Banff, Alberta, Canada, October 17-22, 1982, 1 pp.

24. Gajdusek, D.C., Goldgaber, D. and Millard, E. (1983) Bibliography of Hemorrhagic Fever with Renal Syndrome (Muroid Virus Nephropathy). NIH Publication 83-2603, National Institutes of Health, Bethesda, Maryland, 164 pp.

25. Garruto, R.M. and Dutt, J.S.: Lack of prominent compensatory polycythemia in traditional native Andeans living at 4200 m. American Journal of Physical Anthropology 61, 355-366, 1983.

26. Garruto, R.M., Plato, C.C., Myrianthopoulos, N., Schanfield, M.S. and Gajdusek, D.C.: Blood groups, immunoglobulin allotypes and dermatoglyphic features of patients with amyotrophic lateral sclerosis and parkinsonism-dementia of Guam. American Journal of Medical Genetics 14:2 (February), 289-298, 1983.

27. Garruto, R.M., Yanagihara, R.T., Arion, D.M., Daum, C.A. and Gajdusek, D.C.: Bibliography of Amyotrophic Lateral Sclerosis and Parkinsonism-Dementia of Guam. NIH Publication 83-2622, National Institutes of Health, Bethesda, Maryland, 1983, 167 pp.

28. Gibbs, C.J., Jr.: Perspectives in virus induced slow infections of the central nervous system. In Court, L. and Cathala, F. (Eds.): Virus non conventionnels et affections du systeme nerveux central. Masson, Paris, 1983, pp. 518-528.

29. [Gibbs, C.J., Jr. and Gajdusek, D.C.]: Editorial. Muroid virus nephropathies. Lancet 2:8312 (December 18), 1375-1377, 1982.

30. Gibbs, C.J., Jr., Takenaka, A., Franko, M.C., Gajdusek, D.C., Griffin, M.D., Chields, J., Korch, G.W. and Wartzok, D.: Seroepidemiology of Hantaan virus. Lancet 2:8312 (December 18), 1406-1407, 1982.

31. Goldgaber, D., Lee, P.W., Fukatsu, R., Amyx, H.L., Gibbs, C.J., Jr., Gajdusek, D.C. and Lee, H.-W.: Reovirus type 2 in strains of Korean haemorrhagic fever virus. Lancet 1:8282 (May 22), 1184-1185, 1982.

32. Goldgaber, D., Lee, P.-W., Gibbs, C.J., Jr. and Gajdusek, D.C.: Quantitation of Hantaan virus infectivity, antigen and antibody by immunoenzyme methods. Abstract No. 94 in Abstracts of the First International Symposium on Public Health in Asia and the Pacific Basin, Honolulu, March 7-11, 1983, no pp.

33. Goudsmit, J., Rohwer, R.G., Silbergeld, E.K., Neckers, L.M. and Gajdusek, D.C.: Scrapie in hamsters: clinical disease and disturbances in the serotonergic pathway. In Court, L. and Cathala, F. (Eds.): Virus non conventionnels et affections du systeme nerveux central. Masson, Paris, 1983, pp. 453-463.

34. Gourmelon, P., Amyx, H.L., Breton, P., Court, L. and Gibbs, C.J., Jr.: Alteration du sommeil paradoxal dans la maladie de Creutzfeldt-Jakob experimentale du chat. In Court, L. and Cathala, F. (Eds.): Virus non conventionnels et affections du systeme nerveux central. Masson, Paris, 1983, pp. 363-371.

35. Gourmelon, P., Amyx, H., Court, L., Bassant, M.H., Breton, P., Dormont, D. and Gibbs, C.J., Jr.: La maladie de Creutzfeldt-Jakob experimental du chat: aspect electroencephalographique. Abstract No. 108 in Travaux Scientifiques des Chercheurs du Service de Sante des Armees, No. 3. Direction Centrale du Service de Sante des Armees, Clamart, France, 1982, p. 317.

36. Gourmelon, P., Bassant, M.H., Dormont, D., Court, L. and Gibbs, C.J., Jr.: Modifications electroencephalographiques dans la tremblante experimentale de la souris et du hamster. In Court, L. and Cathala, F. (Eds.): Virus non conventionnels et affections du systeme nerveux central. Masson, Paris, 1983, pp. 372-387.

37. Hoffman, P.M., Pitts, O.M., Rohwer, R.G., Gajdusek, D.C. and Ruscetti, S.K.: Retrovirus antigens in brain of mice with scrapie- and murine leukemia virus-induced spongiform encephalopathy. Infection and Immunity 38:1 (October), 396-398, 1982.

38. Kuroda, Y., Gibbs, C.J., Jr., Amyx, H.L. and Gajdusek, D.C.: Creutzfeldt-Jakob disease in mice: persistent viremia and preferential replication of virus in low-density lymphocytes. Infection and Immunity 41:1 (July) 154-161, 1983.

39. Kingsbury, D.T., Amyx, H.L. and Gibbs, C.J., Jr.: Biophysical properties of the Creutzfeldt-Jakob disease agent. In Court, L. and Cathala, F. (Eds.): Virus non conventionnels et affections du systeme nerveux central. Masson, Paris, 1983, pp. 125-137.

40. Lee, P.W., Amyx, H.L., Gajdusek, D.C., Yanagihara, R.T., Goldgaber, D. and Gibbs, C.J., Jr.: New haemorrhagic fever with renal syndrome-related virus in indigenous wild rodents in the United States. Lancet 2:8312 (December 18), 1405-6, 1982.

41. Lee, P.-W., Amyx, H.L., Salazar, A., Reiner, B., Gibbs, C.J., Jr. and Gajdusek, D.C.: Passive protection and chemotherapy of experimental Hantaan virus infection in laboratory rats. Abstract No. 78 in Abstracts of the First International Symposium on Public Health in Asia and the Pacific Basin, Honolulu, March 7-11, 1983, no pp.

42. Lee, P.-W., Amyx, H.L., Yanagihara, R.T., Goldgaber, D., Gajdusek, D.C. and Gibbs, C.J., Jr.: Isolation of a new hemorrhagic fever with renal syndrome (HFRS)-related virus (Prospect Hill virus) from Microtus pennsylvanicus trapped in the United States and propagation of the virus in vivo and in vitro. Abstract No. 116 in Abstracts of the First International Symposium on Public Health in Asia and the Pacific Basin, Honolulu, March 7-11, 1983, no pp.

43. Lee, P.W., Goldgaber, D., Gibbs, C.J., Jr., Gajdusek, D.C., Yanagihara, R.T., Svedmyr, A., Hlaca, D., Veseniak-Hiran, J. and Glick, A.: Other serotypes of haemorrhagic fever with renal syndrome viruses in Europe. Lancet 2:8312 (December 18), 1405-1406, 1982.

44. Lee, P.W., Svedmyr, A., Amyx, H.L., Gajdusek, D.C., Gibbs, C.J., Jr., Lofgren, O. and Nystrom, K.: HFRS antigen and antibody in two species of Swedish voles. Scandanavian Journal of Infectious Diseases 14:4, 315-316, 1982.

45. Lee, P.W., Yanagihara, R., Amyx, H.L., Goldgaber, D., Franko, M., Gibbs, C.J., Jr. and Gajdusek, D.C.: Hemorrhagic fever with renal syndrome (HFRS) in North America: Commensal infection of wild rodents in the United States with two different HFRS-related viruses. Abstract in Abstracts of the International Conference on Comparative Virology, Banff, Alberta, Canada, October 17-22, 1982, 1 pp.

46. Merz, P.A., Rohwer, R., Somerville, R., Wisniewski, H.M., Gibbs, C.J., Jr. and Gajdusek, D.C.: Scrapie associated fibrils in human Creutzfeldt-Jakob Disease. Abstract No. 68 Abstracts of the Fifty-ninth Annual Meeting of the American Association of Neuropathologists, St. Louis, June 9-12. Journal of Neuropathology and Experimental Neurology 42:3 (May), 327. 1983.

47. Moreau-Dubois, M.-C., Brown, P. and Gajdusek, D.C.: La fusion cellulaire dans l'etude des encephalopathies spongiformes. In Court, L. and Cathala, F. (Eds.): Virus non conventionnels et affections du systeme nerveux central. Masson, Paris, 1983, pp. 164-173.

48. Plato, C.C. and Garruto, R.M.: Collection and recording of dermatoglyphic data. Abstract in Abstracts of the Fifty-second Annual Meeting of the American Association of Physical Anthropologists, Indianapolis, April 7-9, 1983. American Journal of Physical Anthropology 60:2 (February), 239, 1983.

49. Plato, C.C., Garruto, R.M., Yanagihara, R.T., Chen, K.-M., Wood, J.L., Gajdusek, D.C. and Norris, A.H.: Cortical bone loss and measurements of the second metacarpal bone. I. Comparisons between adult Guamanian Chamorros and American Caucasians. American Journal of Physical Anthropology 59:4 (December), 461-465, 1982.

50. Raverdy, Ph., Hauw, J.J., Cathala, F., Remy, A., Brown, P., Ernest, A.M. and Perie, G.: Maladie de Creutzfeldt-Jakob ayant evolue 34 mois chez une femme de 26 ans. Revue Neurologie (Paris) 139:5, 381-383, 1983.

51. Rohwer, R.G.: Scrapie inactivation kinetics: an explanation for scrapie's apparent resistance to inactivation, a reevaluation of estimates of its small size. In Court, L. and Cathala, F. (Eds.): Virus non conventionnels et affections du systeme nerveux central. Masson, Paris, 1983, pp. 84-113.

52. Salazar, A.M., Gibbs, C.J., Jr., Gajdusek, D.C. and Smith, R.A.: Clinical usage of interferons: Central nervous system. In Came, P. and Cater, W. (Eds.): Handbook of Experimental Pharamacology, Vol. 71, Interferon", Chapter 23. Springer-Verlag, Heidelberg, 1983, pp. 471-488.

53. Salazar, A.M., Masters, C.L., Gajdusek, D.C. and Gibbs, C.J., Jr.: Syndromes of amyotrophic lateral sclerosis and dementia: Relation to transmissible Creutzfeldt-Jakob disease. Annals of Neurology 14:1 (July), 17-26, 1983.

54. Scrimgeour, E.M., Masters, C.L., Alpers, M.P., Kaven, J. and Gajdusek, D.C. A clinico-pathological study of a case of kuru. Journal of the Neurological Sciences 59:2, 265-275, 1983.

55. Stratte, P.T., Miller, R.A., Amyx, H.L., Asher, D.M. and Levy, R.: In vivo effects of murine monoclonal anti-human T cell antibodies in subhuman primates. Journal of Biological Response Modifiers 1:2, 137-148, 1982.

56. Svedmyr, A., Lee, P.W., Goldgaber, D., Yanagihara, R., Gajdusek, D.C., Gibbs, C.J., Jr. and Nystrom, K.: Antigenic differences between European and East Asian Strains of HFRS virus. In Proceedings of the Eighth International Congress of Infectious and Parasitic Diseases, Stockholm, June 7-11. Scandinavian Journal of Infectious Diseases, Suppl. 36, 86-87, 1982.

57. Ueda, T., Chen, K-M, Gajdusek, D.C., and Hayama, T.: The significance of motor neuron involvement in parkinsonism-dementia of Guam. Abstract in Abstracts of the Sixth Asian and Oceanian Congress of Neurology, Taipei, Taiwan. November 13-17, 1983.

58. Yanagihara, R.T., Garruto, R.M. and Gajdusek, D.C.: Epidemiological surveillance of amyotrophic lateral sclerosis and parkinsonism-dementia in the Commonwealth of the Northern Marianas Islands. Annals of Neurology 13:1 (January), 79-86, 1983.

59. Yanagihara, R., Lee, P.-W., Diwan, A.R., Gajdusek, D.C. and Gibbs, C.J., Jr.: Seroepidemiology of Hantaan virus infection in Southeast Asia and Oceania. Abstract No. 144 in Abstracts of the First International Symposium on Public Health in Asia and the Pacific Basin, Honolulu, March 7-11, 1983. no pp.

60. Yoshimasu, F., Yasui, M., Yase, Y., Uebayashi, Y., Tanaka, S., Iwata, S., Sasajima, K., Gajdusek, D.C., Gibbs, C.J., Jr. and Chen, K.-M.: Studies on amyotrophic lateral sclerosis by neutron activation analysis. 3. Systemic analysis of metals on Guamanian ALS and PD cases. Folio Psychiatrica et Neurologica Japonica 36:2, 173-179, 1982.

Amyx, H.L., Salazar, A.M., Gajdusek, D.C., and Gibbs, C.J. Jr. (in press) Chemotherapeutic trials in experimental slow virus disease. Abstract, American Association of Neurologists Annual Meeting.

Aoki, T., Drachman, D.B., Asher, D.M., Gibbs, C.J. Jr., Bahmanyar, S., and Wolinsky, J.S. (in press) Attempts to implicate viruses in myasthenia gravis. Archives of Neurology.

Asher, D.M., Gibbs, C.J. Jr., and Gajdusek, D.C. (in press) Slow viruses: Safe handling of the agents of spongiform encephalopathies. In: Manual of Laboratory Safety, D. Groschel, editor. American Society for Microbiology, Washington.

Asher, D.M., Kaufmann, C.A., Kleinman, J.E., Weinberger, D., Gibbs, C.J. Jr., and Gajdusek, D.C. (in press) Attempts to transmit schizophrenia to animals. Abstract at American Psychiatric Association Meeting, Los Angeles, May 5-11, 1984.

Bahmanyar, S., Liem, R.K.H., Griffin, J.W., and Gajdusek, D.C. (in press) Characterization of antineurofilament autoantibodies in Creutzfeldt-Jakob disease. Journal of Neuropathology and Experimental Neurology.

Bahmanyar, S., Williams, E.S., Johnson, F.B., Young, S., and Gajdusek, D.C. (in press) Amyloid plaques in spongiform encephalopathy of mule deer. Journal of Comparative Pathology.

Benfante, R.J. and Gajdusek, D.C. (in press) Antibody studies in the kuru region. II. Respiratory Viruses. Papua New Guinea Medical Journal.

Brown, P. (in press) Acute viral encephalitis. In "Current Diagnosis 7", R.B. Conn, editor.

Brown, P. (in press) Biologic and chemotherapeutic forays into the field of unconventional viruses. In: "Targets for the Design of Antiviral Agents", E. De Clerq and R.T. Walker, editors (Proceedings of NATO Advanced Study Institute, 19 June-2 July 1983, Les Arcs, France). Plenum Publications, New York, 1984, pp. 131-158.

Brown, P. and Asher, D.M. (in press) Subacute and chronic viral encephalitis and encephalopathy. In "Current Diagnosis 7", R.B. Conn, editor.

Brown, P., Rodgers-Johnson, P., Cathala, F., Gibbs, C.J. Jr., and Gajdusek, D.C. (in press) Creutzfeldt-Jakob disease of long duration: clinical-pathological characteristics, transmissibility, and differential diagnosis. Annals of Neurology.

Brown, P., Rohwer, R.G., Amyx, H.L., Gibbs, C.J. Jr., and Gajdusek, D.C. (in press) New data and recommendations for the decontamination of Creutzfeldt-Jakob disease and scrapie virus-infected materials. Abstract, American Society of Virology, July 23, 1984.

Brown, P., Rohwer, R.G., Amyx, H.L., Gibbs, C.J. Jr., and Gajdusek, D.C. (in press) New data and recommendations for the decontamination of CreutzfeldtJakob disease and scrapie virus-infected materials. Abstract presented at the Sixth International Congress of Virology, Sendai, Japan, September 1-7, 1984.

Brown, P., Rohwer, R.G., and Gajdusek, D.C. (in press) Sodium hydroxide decontamination of Creutzfeldt-Jakob disease virus. Letter to the Editor. New England Journal of Medicine.

Brown, P.W., Smallwood, L.A., Gerety, R.J., Breguet, G., Ney, R., and Gajdusek, D.C. (in press) The seroepidemiology of viral hepatitis in Bali, Indonesia. Southeast Asian Journal of Tropical Medicine and Public Health.

Coker-Vann, M., Brown, P., and Gajdusek, D.C. (in press) Serodiagnosis of human cysticercosis using a chromatofocused antigenic preparation of Taenia solium cysticerci in an enzyme-linked immunosorbent assay (ELISA). Transactions of the Royal Society of Tropical Medicine and Hygiene.

Constans, J., Viau, M., Garruto, R.M., Gajdusek, D.C., and Spees, E.K. (in press) Polymorphism of serum vitamin D-binding protein in humans. An anthropological analysis of the distribution of the different alleles. Science.

Doi, H., Chen, K.-M., Chase, T.N., Yanagihara, R.T., and Uebayashi, Y. (in press) Effect of L-dopa on clinical duration and quality of life in parkinsonism dementia of Guam. Rinsho Shinkeigaka.

Fetchko, P. (in press) The Gajdusek collection of primitive art. 1984 revised edition.

Fukatsu, R., Amyx, H.L., Gibbs, C.J. Jr., and Gajdusek, D.C. (in press) Development of cerebral amyloid plaques in experimental murine scrapie. American Association of Neuropathologists.

Fukatsu, R., Pocchiari, M., Aoki, T., Sotelo, J., Gibbs, C.J. Jr., and Gajdusek, D.C. (in press) Ultrastructural studies on synaptic formations in dissociated fetal mouse brain cultures. Neuroscience Letters.

Gajdusek, D.C. Forward. In "Medicina Tropical en America Latina", G. Toro, G. Roman, and L.N. Roman, editors. Bogota, 1983, 196 pgs.

Gajdusek, D.C. (in press) Subacute spongiform virus encephalopathies caused by unconventional viruses. Chapter in "Subviral Pathogens of Plants and Animals: Viroids and Prions", edited by Karl Maramorosch and J. McKelvey, Jr. Academic Press. 1984.

Gajdusek, D.C. (in press) Unconventional viruses. Chapter. In "Concepts in Viral Pathogenesis", edited by A. Notkins and M. Oldstone. Springer Verlag, 1984.

Gajdusek, D.C. (in press) Environmental factors provoking physiological changes which induce motor neuron disease and early neuronal aging in high incidence foci in the Western Pacific: Calcium deficiency induced secondary hyperparathyroidism and resultant CNS deposition of calcium and other metallic cations as the cause of ALS and PD in high incidence foci. Motor Neuron Disease Association International Symposium on Progress in Motor Neuron Disease, London, July 5-7, 1982, London.

Gajdusek, D.C. (in press) Unconventional virus infections. In "Human Viral Infections", B.N. Fields, J.L. Melnick, R. Chanock, R.E. Shope, and B. Roizman, editors.

Gajdusek, D.C. and Gibbs, C.J. Jr. (in press) Chapter in Intramural History of NIH. History of slow virus research at NIH. Monograph edited by Dewitt Stetton.

Gajdusek, D.C., Goldfarb, L.G., and Millard, E. (in press) Bibliography of Viliuisk Encephalitis.

Garruto, R.M. (in press) Environmental challenge--biocultural response: the concept of optimal and critical levels in adaptation of man to the natural environment. Symposium on Human Adaptation to the Environment: Relative Impacts of Physical, Environmental and Sociocultural Factors. Vancouver, August 20-25, 1983.

Garruto, R.M. (in press) Health consequences of migration in Micronesia. In Proceedings of the Conference on Migration and Adaptation to Environmental Change Among Pacific Populations. East-West Center Press, University of Hawaii, Honolulu.

Garruto, R.M. (in press) Polycythemia, altitude and human adaptation. Proceedings of the Conference on Human Genetics and Adaptation, Indian Statistical Institute, Calcutta.

Garruto, R.M. (in press) Population Isolates: natural experimental phenomena of importance to human biology and medicine. Abstract, Seventeenth Annual Meeting Society for Epidemiology and Research, June 13-15, 1984. Houston. American Journal of Epidemiology.

Garruto, R.M., Fukatsu, R., Yanagihara, R., Gajdusek, D.C., Hook, G., and Fiori, C.E. (in press) Imaging of calcium and aluminum in neurofibrillary tangle-bearing neurons in parkinsonism-dementia of Guam. Proceedings of the National Academy of Sciences.

Garruto, R.M. and Gajdusek, D.C. (in press) Pacific cultures: a paradigm for the study of late-onset neurological disorders. In: "Risk Factors for Senility", H. Rothschild, editor. Oxford University Press.

Garruto, R.M., Yanagihara, R.T., and Gajdusek, D.C. (in press) Disappearance of high incidence amyotrophic lateral sclerosis and Parkinsonism-dementia on Guam. Neurology.

Gibbs, C.J. Jr. (in press) Creutzfeldt-Jakob disease and other presenile dementias. Chapter 246 in "Neurosurgery", Robert H. Wilkins and Setti S. Rengachary, editors. McGraw-Hill.

Gibbs, C.J. Jr., Amyx, H.L., Asher, D.M., Kobrine, A., Bernoulli, C., and Gajdusek, D.C. (in press) Transmission of Creutzfeldt-Jakob disease to a chimpanzee by implanted electrodes. Lancet.

Gibbs, C.J. Jr. and Asher, D.M. (in press) Slow virus infections of central nervous system. In: "Control of Communicable Diseases in Man", 14th Edition. American Public Health Association.

Gibbs, C.J. Jr., Masters, C.L., and Gajdusek, D.C. (in press) Virus-induced slow degenerations of the central nervous system and related diseases. Chapter 12 in "Update on the Zoonoses," W.T. Hubbert and P. Schurenberger, editors.

Hook, J.J., Fiori, C., Gorlen, K., Gibson, C.G., Garruto, R.M., Fukatsu, R., Yanagihara, R., and Gajdusek, D.C. (in press) Elemental imaging of brain tissue using a computer controlled electron beam x-ray microanalyzer. Abstract in Conference on Aluminum Analysis in Biological Materials. Charlottesville, Virginia, June 29-30, 1983.

Iqbal, K., Wisniewski, H.M., Garruto, R.M., Masters, C.L., and Gajdusek, D.C. (in press) Guam Parkinsonism dementia: activities of cholinergic and GABAergic enzymes in brain. Presented at Annual Meeting of the American Association of Neuropathologists, June 14-17, 1984, San Diego. In: Journal of Neuropathology and Experimental Neurology.

Klitzman, R.L., Alpers, M.P., and Gajdusek, D.C. (in press) The natural incubation period of kuru and the epidoses of transmission in three clusters of patients. Neuroepidemiology.

Lee, P.W., Amyx, H.L., and Gajdusek, D.C. (in press) The susceptibility of nude mice to Hantaan virus. Proceedings of the Society of Experimental Biology and Medicine.

Lee, P.W., Amyx, H.L., and Gajdusek, D.C. (in press) The use of the athymic nude mouse in Hantaan virus studies. Infection and Immunity.

Masters, C.L., Rohwer, R.G., Franko, M.C., Brown, P.W., and Gajdusek, D.C. (in press) The sequential development of spongiform change and gliosis of experimental scrapie in the golden syrian hamster. Journal of Comparative Pathology.

Masullo, C., Pocchiari, M., Lust, W.D., Gibbs, C.J. Jr., and Gajdusek, D.C. (in press) GABAergic system in scrapie infected hamsters. Abstract presented at the Society for Neuroscience Annual Meeting, November 6-11, 1983.

Merz, P.A., Rohwer, R., Kascsak, R., Wisniewski, H.M., Somerville, R.A., Gibbs, C.J. Jr., and Gajdusek, D.C. (in press) An infection specific particle from the unconventional slow virus diseases. Science.

Mori, S., Gibbs, C.J. Jr., Amyx, H.L., and Gajdusek, D.C. (in press) Easy susceptibility of newborn mice to scrapie agents and the absence of vertical transmission of scrapie in mice. Abstract, Sixth International Congress on Virology, Sendai, Japan. September 1-7, 1984.

Nakamura, T., Gibbs, C.J. Jr., Yanagihara, R., Amyx, H.L., Lee, P.W., and Gajdusek, D.C. (in press) Differential susceptibility of immunocompetent and immunodeficient suckling mice to Hantaan virus infection. Journal of Virology.

Plato, C.C., Fox, K.M., and Garruto, R.M. (in press) Measures of lateral functional dominance: foot preference, eye preference, digital interlocking, arm folding and foot overlapping. Human Biology.

Plato, C.C., Fox, K.M., and Garruto, R.M. (in press) Measures of lateral functional dominance: hand dominance. Human Biology.

Plato, C.C., Garruto, R.M., and Gajdusek, D.C. (1983) Further studies on the genetics of the Chamorros of Guam: dermatoglyphics. Human Heredity, 293.

Plato, C.C., Garruto, R.M., and Fox, K.M. (in press) Amyotrophic lateral sclerosis and Parkinsonism-dementia of Guam: a 25 year prospective patient-control study. Abstract Seventeenth Annual Meeting Society for Epidemiological Research, June 13-15, 1984. Houston, Texas. American Journal of Epidemiology.

Pocchiari, M., Masullo, C., Vaccarino, F., Gibbs, C.J. Jr., and Gajdusek, D.C. (in press) Depression of the GABAergic system in scrapie infected hamsters. Brain Research.

Rohwer, R.G. (in press) Scrapie. Virus-like size and susceptibility to inactivation of the infectious virus-like agent. Nature.

Rohwer, R.G. and Gajdusek, D.C. (in press) Growth kinetics of hamster scrapie strain 263K: sources of slowness in a slow virus infection. Virology.

Rodgers-Johnson, P., Garruto, R.M., Gajdusek, D.C., and Chen, K.-M. (in press) Changing clinical characteristics in Guamanian amyotrophic lateral sclerosis and parkinsonism dementia: a 30 year reevaluation.

Salazar, A.M., Gibbs, C.J. Jr., and Gajdusek, D.C. (in press) Viral and immune mechanisms of demyelination. In: "Demyelinating Diseases", A. Lowenthal, J.J. Martin and A. Neetens, editors. Belgian Opthalmological Society, Antwerp.

Salazar, A.M., Gibbs, C.J. Jr., and Gajdusek, D.C. (in press) Viral and immune mechanisms of demyelination. In: "Demyelinating Diseases", A. Lowenthal, J.J. Martin and A. Neetens, editors. Belgian Opthalmological Society, Antwerp.

Simmons, R.T., Gravdon, J.J., Rodrique, R.R., Ziqas, V., and Gajdusek, D.C. (in press) Blood group genetic data from the Southern and Western Highlands Districts and the Western District, Papua New Guinea. American Journal of Physical Anthropology.

Takenaka, A., Gibbs, C.J. Jr., Franko, M.C., Gajdusek, D.C. and Griffin, M.D. (in press) Antibodies to Hantaan virus in renal transplant candidates. Journal of Infectious Diseases.

Takenaka, A., Gibbs, C.J. Jr., and Gajdusek, D.C. (in press) A plaque assay for quantitation of Hantaan virus infectivity and measurement of anti-viral neutralizing antibody. Journal of Infectious Diseases.

Takenaka, A., Gibbs, C.J. Jr., Nakamura, T., and Gajdusek, D.C. (in press) Replication of Hantaan virus in human leukocytes. Journal of Virology.

Uebayashi, Y., Chen, K-M, Gajdusek, D.C., and Gibbs, C.J. Jr.: Amyotrophic lateral sclerosis: long-surviving cases on Guam. Journal of Neuroepidemiology (in press).

van der Waals, F.W., Pomeroy, K.L., Goudsmit, J., Asher, D.M., and Gajdusek, D.C. (in press) Antibodies to hemorrhagic fever in Grand Bassa County, Liberia. Congress of Virology, 1984.

Yanagihara, R.T., Chin, C.-T., Gajdusek, D.C., Gibbs, C.J. Jr., Diwan, A., Poland, J.B., Kleeman, K.T., Wilfert, C.M., Meiklejohn, T., and Glezen, W.P. (in press) Prevalence of antibody against Hantaan virus in patients with febrile illness in United States. New England Journal of Medicine.

Yanagihara, R., Grafton, D.A., Garruto, R.M., and Gajdusek, D.C. (in press) Elemental content of scalp hair in Guamanian Chamorros with amyotrophic lateral sclerosis and parkinsonism-dementia. Archives of Neurology.

Yanagihara, R.T., Svedmyr, A., Amyx, H.L., Lee, P.W., Goldgaber, D., Gajdusek, D.C., Gibbs, C.J. Jr., and Nystrom, K. (in press) Nephropathia epidemica: isolation and propagation of the causative virus in bank voles and mongolian gerbils. Journal of Infectious Diseases.

Yanagihara, R.T., Traub, R.D., Gajdusek, D.C., Chin, C.-T., and Gibbs, C.J. Jr. (in press) Prospect Hill virus: serological evidence for infection in mammalogists. New England Journal of Medicine.

Zaninovic, V., Barreto, P., Biojo, R., and Gajdusek, D.C. (in press) A high incidence focus of non inherited spastic paraparesis in the South Pacific coast of Colombia. Annals of Neurology.

CONTRACTS

Gulf South Research Institute
New Iberia, Louisiana

Contract #N01-NS-8-09931

$ 600,000.00

Public Health Research Institute of the City of New York, Inc.
Otisville, New York

Contract #N01-NS-7-0082

$ 131,000.00

Litton Bionetics, Inc.
(Administration by NCI)

Contract #N01-CO-75380

$ 420,000.00

Mrs. Elisabeth Beck
Institute of Psychiatry
London, England

Contract #263-78-C-0049

$ 24,500.00

ANNUAL REPORT

October 1, 1982 through September 30, 1983

Laboratory of Molecular Biology
National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

Annual Report
October 1, 1982 through September 30, 1983
Laboratory of Molecular Biology
National Institutes of Neurological and Communicative Disorders and Stroke

Ernst Freese, Chief

The laboratory has examined the initiation of meiosis and differentiation (sporulation) in eukaryotic yeast and sporulation in prokaryotic bacteria. Use of these organisms has the advantage that their genetic and biochemical properties are the best known among all differentiating organisms. The results show a strong similarity among the compounds controlling the initiation of this type of differentiation - thus suggesting that the initiation mechanisms may be related in evolution. Some reactions related to differentiation have been examined in more detail, in particular, the gene for glucose dehydrogenase, a typical developmental enzyme, was cloned. In mammalian cells, the properties and synthesis of receptors and transport systems for biogenic amines have been investigated. Studies on the effect of teratogens on mouse embryo cultures showed numerous differences in the protein patterns of normally developing embryos versus those exposed to a teratogenic compound.

1. Control of bacterial differentiation (sporulation) by GTP and methylation. Differentiation of microbes and omnipotent cells of higher organisms is generally initiated by nutritional deprivation. In Bacillus subtilis, the Laboratory has demonstrated that any conditions causing massive differentiation (sporulation) also cause a decrease of the intracellular GTP concentration below a critical value, which is about 30% below the normal concentration. This can be achieved by general nutritional deprivation, by the addition of specific inhibitors of GMP synthesis, by guanine starvation of guanine auxotrophs, or by the "stringent response" to partial amino acid deprivation. Several antibiotics prevent sporulation resulting from the stringent response but addition of decoyinine, an inhibitor of GMP synthetase, restores sporulation. It was also shown that the uptake systems for some compounds disappear under certain sporulation conditions, making it possible for cells to continue the spore development - once it has been started - even when their environment changes so that they would otherwise not have entered this development under the new conditions. For example, as a result of the stringent response the concentration of GMP, and thus GTP, decreases and sporulation begins. Addition of guanine does not interfere because the stringent response also abolishes guanine uptake. However, the change of these uptake systems is not necessary under all sporulation conditions.

There are some mutants which continually enter sporulation at a high frequency while the cells are growing in the normal growth medium. In some strains, this effect results from a mutation (spd) causing such a mild deficiency of aspartate that the cells grow normally but produce a slight stringent response (due to a small percentage of uncharged asp-tRNA) which in turn caused sporulation. In relaxed (relA) mutants lacking the stringent response, the phenomenon was abolished. Other spd mutations caused continual

sporulation even in strains with the rel background. Some of them were resistant to ethionine, which suggests an involvement of methylation in the control of sporulation. However, partial deprivation of methionine (in a rel mutant) did not cause sporulation nor did the addition of methionine prevent the sporulation caused by GTP deprivation. Thus the effects of GTP and methylation are separable. Addition of ethionine to a partially resistant (eth) mutant greatly increased the frequency at which cells continually entered sporulation. Ethionine is converted into S-adenosylethionine which either inhibits methylation by SAM or causes its effect by ethylating rather than methylating some molecules such as DNA. Mutants altered in the DNA methylation or restriction activity were examined, and again quantitative differences concerning the frequency of spontaneous or induced (by decoyinine) sporulation were observed. Thus DNA methylation seems to control the extent to which differentiation is repressed in growing cells, whereas the signal controlling the onset of massive differentiation is GTP (or GDP). Attempts to identify the relevant GTP binding protein are under way.

2. Control of meiosis and sporulation in yeast. The eukaryotic yeast Saccharomyces cerevisiae can sporulate only when the cells are in the diploid (a α) form. As a result of nutrient starvation, the cells first pass through meiosis, including genetic recombination, before the four haploid nuclei each give rise to a spore. Because millions of cells per ml enter this differentiation process, S. cerevisiae provides an ideal system to study meiosis and its abnormalities which, in humans, lead to severe defects (e.g. Down's Syndrome). The laboratory has shown that these cells sporulate when any one of the major nutrients (readily metabolizable carbon, nitrogen, phosphorous or sulfur compounds) become scarce. With the exception of nitrogen compounds, enough of which can accumulate in cells grown in a rich medium, the compounds must remain available in the medium thus allowing a slow cellular metabolism. All these conditions lead to a decrease in the concentration of GTP. Further studies with specific inhibitors and mutants (including a guanine auxotroph) have shown that the partial deprivation of purine nucleotides and most effectively the specific deprivation of guanine nucleotides, e.g. GTP, cause meiosis and sporulation, whereas the specific deprivation of pyrimidine nucleotides (in uracil auxotrophs) does not. The most effective inducer was virazole (=ribavirin) which is presently used against virus infections such as Herpes.

The partial deprivation of sulfur or of methionine causes sporulation and produces a decrease in the intracellular concentration of both SAM and GTP. A decrease of SAM was also obtained whenever the concentration of GTP decreased, presumably because GTP is a precursor of folate which is needed to synthesize methionine. This decrease was avoided by the addition of methionine. Methionine also inhibited the sporulation caused by guanine deprivation. However, in the presence of methionine, the cellular concentration of SAM was 14 times higher than in normal cells and high SAM concentrations are known to produce general metabolic inhibition. It will be necessary to use additional mutations in order to determine whether yeast meiosis and sporulation is initiated by the GTP decrease - while high concentrations of SAM simply inhibit sporulation and undermethylation (of DNA) only decreases the threshold of response to partial GTP deprivation - or whether this differentiation is initiated by undermethylation (e.g. of DNA) alone.

3. Control of developmental enzymes and cloning of a developmental gene. One of the early events in the sporulation of Bacilli is the arrest of cell

wall synthesis and turnover while the asymmetric membrane septum is being layed down. Although they are both caused by GTP deprivation, the two processes are not always correlated because wall synthesis (but not cell lengthening or crosswall formation) continues when turnover has been arrested, and inhibition of wall synthesis has only a mild effect on turnover. Since the precursors of cell wall are still made during GTP deprivation, wall synthesis apparently is controlled at the level of polymerization. Wall turnover may be a measure of the activity of wall hydrolases needed for lateral cell wall expansion which results from insertion of new peptidoglycan chains (in contrast to the extension of old chains). When measured under many different growth conditions, the turnover rate was nearly proportional to the growth rate of the cell; the ratio of these rates being only slightly higher for rapidly growing than for slowly growing cells. The correlation with growth suggests that wall turnover depends on the liberation of hydrolytic enzymes from their associated inhibitor (teichoic acid) by mechanical separation during wall expansion. In contrast to conventional beliefs, wall turnover and autolysis were not correlated.

Whereas the mechanisms controlling enzyme induction and repression are reasonably well understood, it is not known how cells prevent the expression of developmental genes until they are needed at a particular stage of differentiation. The gld gene for glucose dehydrogenase of B. subtilis is such a developmental gene; it is transcribed and translated only during sporulation and only in the forespore cell compartment, which is located inside the mother cell and surrounded by two membranes with opposite polarity. The gene together with its control (promoter) region has been cloned in various plasmids. All plasmids able to grow in E. coli produced the enzyme in E. coli; in B. subtilis a shuttle plasmid with a high copy number produced a small amount of enyzme, whereas a plasmid with a low copy number produced almost no enzyme. This suggests the presence of a repressor which can be titrated out by a large amount of DNA containing the gld operon. Using transposon insertion and transduction, the gld gene has been mapped on the chromosome and mutants deficient in glucose dehydrogenase have been isolated. Following restriction analysis, the gene is now being sequenced (by the dideoxy method in M13). In vitro experiments have shown that the gene can be transcribed only by a minor RNA polymerase fraction (using the sigma-37 factor). Further studies will involve isolation of mutants constitutive for the production of the enzyme even in vegetative cells, identification of the promoter and a possible operator site on DNA, and in vitro analysis using different RNA polymerases and cellular fractions of B. subtilis containing a possible repressor or inducer.

4. Synthesis and specificity of neuro-receptor proteins and analysis of proteins in mouse embryo cultures. The aim of this work was to define the biochemical reactions by which cell surface receptors for hormone/neurotransmitters convey information across the plasma membrane. Earlier experiments in this laboratory have shown that butyrate induces the synthesis of beta-adrenergic and benzodiazepine receptors and of adenylate cyclase in human cell lines (e.g. HeLa). It has now been demonstrated that certain nucleosides also induce the synthesis of beta-adrenergic receptors. When one of these compounds was used first and cells were then treated with butyrate (in the absence of the nucleoside), three times more receptors were made than would be expected from an additive effect. One of the inducing compounds was 5-azadeoxycytidine, which is also incorporated into DNA and causes its under-

methylation and which induces the synthesis of various developmental proteins. However, since the other nucleosides that act as inducers of these receptors (e.g. cytosine arabinoside) do not cause undermethylation, it is unlikely that undermethylation is responsible for the induction of the beta-adrenergic receptors.

Evidence for a previously undescribed transport system for catecholamines has been obtained in HeLa cells. The receptor for this system is distinct from that for alpha- and beta-adrenergic receptors, and catecholamine transport depends on the proton pump, which is apparently energized by ATP. In this respect the transport sites resemble those of chromaffin cells of the adrenal medulla. However, in contrast to chromaffin cells, HeLa cells do not have serotonin binding sites although imipramine can bind to them and competes with catecholamine transport. Therefore, imipramine apparently can bind not only to the serotonin sites found in CNS tissue but also to certain catecholamine binding sites.

Earlier studies on the effect of certain teratogens on the post-implantation embryo cultured in vitro have now been completed. For this final phase, 2-dimensional acrylamide gel patterns of embryo proteins were examined by a refined silver staining technique permitting the detection of as little as 6 pg of protein per spot. Computer assisted analysis of the gels showed excellent reproducibility. Significant differences were observed between embryos grown in the presence and absence of valproate. The technique should be useful in the detection of minor or highly specific teratogenic effects.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02365-05 LMB

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Intercellular Communications and Transmembrane Signals

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
R.C. Henneberry, Chief, MNS, 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:
3.9	2.3	1.6

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The major goal of this project is to better understand the response of individual mammalian cells to extracellular signals. We have previously described modulation of hormone/neurotransmitter receptors on cultured human cells by manipulation of medium components and induction of receptor synthesis and expression by short-chain fatty acids (e.g. butyrate). During this reporting period we have continued to emphasize the growth of human cells in serum-free, chemically-defined media; this approach permits experimentation which is not feasible in the presence of serum. For example, our finding of a role for epidermal growth factor in the maintenance of beta-adrenergic recptor expression could only have occurred in serum-free media. We have recently found a strong synergistic effect on beta-adrenergic receptor induction between butyrate and the nucleoside analogue 5-azacytidine which has been reported to induce differentiation by a mechanism involving DNA hypomethylation. However, we have also found comparable synergism with a variety of similar analogues including many which do not cause DNA hypomethylation; these findings should permit further understanding of regulation of receptor synthesis and the mechanism(s) of induction by fatty acids and nucleoside analogues. We have also found a transport site for catecholamines with a unique and previously undescribed specificity, distinct from both alpha- and beta-adrenergic receptors, on cultured human cells; transport at this site is dependent on an electrochemical proton gradient across the plasma membrane. Due to the direction in which this project has evolved in the last few years, with increased emphasis on cellular physiology, the project in its present form will be terminated at the end of this fiscal year. Several major aspects of the research will be incorporated into project number Z01 NS 02365-05 LMB which will be retitled and continued in FY84.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 01886-13 LMB

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Control of Meiosis and Morphogenesis

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
E. B. Freese, Biologist, 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:
4.0	4.0	0.0

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Meiosis and sporulation in the eukaryotic yeast Saccharomyces cerevisiae can be initiated by the partial deprivation of purine nucleotides and most effectively by the deprivation of guanine nucleotides (GTP). This was shown by the use of specific auxotrophic mutants or by the addition of specific inhibitors of GMP synthesis, the most effective inducer being virazole (=ribavirin). The differentiation of yeast can also be caused by partial deprivation of sulfur or methionine, both of which result in a decrease of the intracellular concentration of S-adenosyl-methionine (SAM) as well as GTP. As GTP deprivation also produces a decrease in SAM, it is not clear which of the two compounds control sporulation. Experiments are under way to decide that.

To determine which protein changes are involved in meiosis, a method has been developed to isolate large numbers of nuclei rapidly and cleanly. Two-dimensional electrophoresis was used to determine qualitative and quantitative changes in nuclear proteins.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02527-02 LMB

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
The Role of Methylation in Differentiation

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
E. Freese, Chief, 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:
4.2	2.4	1.8

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Mutants resistant to the methionine analog ethionine have been isolated. Three types of mutants have been identified. One type (metT) is deficient in methionine and ethionine uptake, another is deficient in S-adenosyl-methionine (SAM) synthetase, and the third (eth) has an unknown biochemical lesion that enables ethionine to increase the frequency at which cells spontaneously enter sporulation. The 2-3% SAM-synthetase activity produced by the metE mutants suffices to enable SAM synthesis and growth at almost the normal rate. eth metE double mutants are more resistant to ethionine than either mutant alone, and they no longer sporulate at increased frequency upon ethionine addition. Apparently, this increased sporulation is due to the synthesis of S-adenosyl-ethionine, which has been identified by HPLC. In the eth mutant, DNA sites which can be specifically cut by the hsrR restriction endonuclease, are more methylated than in the standard strain. This was shown by the restriction pattern of phi105 phages grown in these strains.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 01244-19 LMB

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Control Mechanisms and Differentiation

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
E. Freese, Chief, LMB, NINCDS

COOPERATING UNITS *(if any)*

Dr. R. Doi	Univ. California, Davis, CA
Dr. N. Vasantha	Genex Corporation, Gaithersburg, MD
Dr. R. Ramaley	Univ. Nebraska Medical Center, Omaha, NB

LAB/BRANCH
Laboratory of Molecular Biology

SECTION
Developmental Biology Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
6.9	5.9	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Sporulation in the prokaryotic Bacillus subtilis can be initiated by the partial deprivation of amino acids, which causes a "stringent response". Certain antibiotics prevented this induction with almost no inhibition of growth. Their effect was counteracted by decoyinine which specifically inhibits the synthesis of guanosine monophosphate (GMP). The stringent response also inhibited the uptake of guanine and uracil, but only the latter was also inhibited by addition of decoyinine alone.

To understand the mechanisms controlling the synthesis of a typical developmental protein, the gene for glucose dehydrogenase of Bacillus subtilis was cloned in several plasmids. In the non-differentiating E. coli, these plasmids caused production of active glucose dehydrogenase during vegetative growth. However, a low copy plasmid shuttle vector produced essentially no glucose dehydrogenase activity in B. subtilis, and a high copy plasmid produced a low amount of enzyme; this suggests the titration of a repressor. In vitro, the gene could be transcribed into RNA, but only by a minor component of RNA-polymerase of B. subtilis which may play a special developmental role.

The turnover of B. subtilis cell wall was measured under many different growth conditions and found to be almost proportional to the growth rate. In various lyt mutants, no correlation between the rate of turnover and that of autolysis was observed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02364-05 LMB

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Development and Teratology in Rodent Embryo Culture

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
R.C. Henneberry, Chief, MNS, LMB, NINCDS

COOPERATING UNITS *(if any)*
Image Processing Section, Laboratory of Pathology, NCI
Office of Biometry and Field Studies, NINCDS

LAB/BRANCH
Laboratory of Molecular Biology

SECTION
Molecular Neurobiology Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.3	1.3	0.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The major goals of this study have been (1) to adapt newly developed methods of embryo culture for teratogenicity studies; (2) to determine the teratogenic potential of several selected drugs; and (3) to evaluate the utility of the embryo culture system for basic studies in developmental biology. These goals have been reached. Mouse embryos in culture have been used to demonstrate dose-dependent teratogenic effects of the anticonvulsants valproic acid and diphenylhydantoin in the absence of maternal modification. The suitability of embryo culture for examining the mechanisn(s) by which drugs elicit teratogenic effects, as well as for applying newly developed methods of computer-assisted analysis of polyacrylamide gels after 2-dimensional electrophoresis to the proteins of a single embryo. Since the original goals of the study have been met, and in order to consolidate the research goals and resources of this section, this project will be terminated at the end of this reporting period. Much of the methodology developed during the course of this project, especially the computer-assisted analysis of 2-dimensional gels, will be incorporated into project number Z01 NS 02365-05 LMB which will be retitled and continued in FY 84.

ANNUAL REPORT

October 1, 1982 through September 30, 1983

Laboratory of Molecular Genetics

National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

ANNUAL REPORT
October 1, 1982 through September 30, 1983
Laboratory of Molecular Genetics
National Institute of Neurological and Communicative
Disorders and Stroke

Robert A. Lazzarini, Chief

1982 was a watershed for the Laboratory of Molecular Genetics. Each of the three sections of the Laboratory made pivotal advances in their programs. In all cases, the successes mark the end of the arduous developmental work and the beginning of the investigative phases.

Recombinant Genetics Section

The climax of a year's effort was a construction and positive identification of a cDNA clone of mouse myelin basic protein (MBP). This represents the first time a gene coding for a myelin constituent has been cloned. Indeed, it is the first time that a gene expressed only in oligodendrocytes has been cloned. The availability of this clone has cracked our research problem wide open. Using this clone, we have isolated the portion of the mouse chromosome that contains the MBP gene and we are presently studying the flanking nucleotide sequences as well as the gene itself. Using our clone, we have demonstrated that there are several species of MBP mRNA and that some of them are astonishingly large (2,300 - 4,300 bases). We have quantitated the amounts of these mRNAs present in mouse brain during the various stages of development and have shown that 18 days after birth is the peak of MBP gene expression.

Of particular importance was our demonstration that the shiverer mutant mouse, which is deficient in its ability to myelinate CNS axons, lacks any detectable MBP mRNA. The fact that no mRNA was found, rather than an inoperative mRNA, suggests that the lesion lies in one of the regions of the mouse chromosome controlling the expression of this gene and does not lie within the gene itself.

Molecular Virology Section

VSV RNA polymerase is an enzyme complex consisting of a very large (L) and a small (NS) protein. This complex catalyzes the synthesis of RNA and its capping, methylation and polyadenylation. We have just succeeded in cloning and sequencing the entire NS and L genes -- about 7,300 bases or 60% of the viral chromosome. From the nucleotide sequence, we have deduced the amino acid sequence of the L protein. This detailed picture of the protein will allow us to map the active sites of this protein and to understand how the various activities of the protein are controlled.

Two new initiatives of this section have had an auspicious beginning. The first is an investigation of the determinants of virus host cell tropism. The initial focus of this study is the characterization of the surface glycoproteins of measles virus which strongly influence the spectrum of host cells to which the virus can bind and ultimately penetrate. We have begun by assembling a library of measles cDNA clones using measles genomic RNA as a

template. Since many of these clones bear information from two or more adjacent genes, analysis of the clones will ultimately yield a genetic map (gene order) of the virus chromosome. We have devised a unique procedure for identifying the genes that are cloned. We sequence the clone, chemically synthesize an oligopeptide specified by it, raise antisera to the peptide and finally identify the clone by determining which measles protein is recognized by the antisera. Following this procedure, we have positively identified clones of the P cistron of measles virus. We plan to "walk along the chromosome" using overlapping clones until we have found hemagglutinin (HA) cistron and the fusion protein cistron. Our initial work has already indicated that the library we have constructed will be more than adequate for our purposes.

The second new initiative of this section is a collaborative effort with the Neural and Molecular Ultrastructure Section of the Laboratory and concerns the assembly of virus particles in infected cells. The progress of this program is summarized below.

Neural and Molecular Ultrastructure Section

The lion's share of our viral assembly program is carried out by this section. During the last year, we have assembled the necessary "high-tech" equipment for microinjection into living cells and low light intensity video microscopy of the injected cells. We have created and characterized panels of monoclonal antibodies and have developed new techniques for the electron microscopic visualization of the assembly of the virus at the inside of the plasma membrane. Using these entirely novel techniques, we have interfered with the viral assembly by microinjecting monoclonal antibodies into living cells and, by doing so, have established that a pool of free (unbound) nucleocapsid proteins exists in the infected cell. With the new electron microscopic techniques, we have visualized viral particles assembling at the cytoplasmic face of the membrane. Presently, we are identifying which viral proteins are present in these particles by immunohistochemistry. I should like to reemphasize that the techniques that we are employing are entirely new and the images that we have obtained of assembling virus particles have never been achieved before.

CONTRACT NARRATIVE
Laboratory of Molecular Genetics
Fiscal Year 1983

UNIVERSITY OF VIRGINIA (NO1 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 DNAs 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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02528-02 LMG

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Regulation of Myelin Synthesis

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Robert A. Lazzarini, Chief, Laboratory of Molecular Genetics, IRP, 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, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
5	3.5	1.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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 mRNAs, and are presently searching among the five hundred library clones in order to identify those which contain the genes for myelin basic proteins. We have tentatively identified several such clones and are characterizing them extensively to establish whether they contain the desired genes.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02026-11 LMG

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Regulation of Viral Nucleic Acid Synthesis in Animal Cells

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

M. Schubert, Senior Staff Fellow, Laboratory of Molecular Genetics, IRP, NINCDS

COOPERATING UNITS *(if any)*

Department of Microbiology and Immunology, Duke University

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

Molecular Virology Section

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
4.75	4.25	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Viral diseases of the central nervous system (CNS) usually occur as a complication rather than a normal consequence of infection. Nevertheless, many members of the myxo-, paramyxo-, arena-, bunya- and rhabdovirus families, either exceptionally or as a normal consequence, infect the CNS, causing encephalitis or meningitis. Despite their importance to medical neurology, very little is known about the regulation and mode of replication of these viruses in the host organism. Furthermore, virus infections also are distinguished in that they frequently elaborate defective interfering (DI) particles and exhibit evidence of autointerference and viral persistency.

The long range objective of this project is the description of the component molecular events involved in the replication of the negative strand viruses. The topics that are currently being investigated are:

1. The origin of DI particles.
2. The primary structure of the gene coding for the VSV L protein (the RNA polymerase).

Toward these ends, we have cloned the L gene using recombinant DNA techniques and have determined the nucleotide sequence of this massive gene (6,400 bases). Analysis of this sequence revealed the primary amino acid sequence of the protein and has identified several regions of the chromosome that are important to DI particle formation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02600-01 LMG

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Assembly of Enveloped RNA Viruses

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

H. Arnheiter, FIC Visiting Associate, Lab. of Molecular Genetics, IRP, 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	6	1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

To understand the molecular events that lead to defective assembly of viral macromolecular components into viral particles, we have recently started to study the normal assembly of two negative stranded RNA viruses, measles virus (known for its neurotropism in humans) and vesicular stomatitis virus, a model virus for the rabies virus (a usually fatal human neuropathogen). Using immunolabeling techniques at the light and electron microscopic level in combination with the quick-freezing, deep etching replica technique, we study localizations and interactions of viral components during acute infection of cultured cells. In order to analyze cellular expressions and processing of viral polypeptides in the absence of productive viral infection, cells are being transfected with eukaryotic expression vectors containing individual viral genes. A battery of monoclonal antibodies and polyclonal rabbit immunoglobulins have been prepared and purified extensively to serve as convenient immunoreagents. For some of the monoclonal antibodies, the exact binding sites have been assigned to particular sequences on the viral polypeptide chains. Of particular concern is the study of the interaction of viral nucleic acids with those proteins assumed to regulate viral transcription and replication. In order to analyze the molecular anatomy and dynamic events of this interaction monoclonal antibodies are introduced into suitable host cells by manual needle microinjection, either prior to or after viral infection of the cells. As a result, a monoclonal antibody to the vesicular stomatitis virus nucleocapsid protein has been found to interfere specifically with the interaction of this protein with viral genomic RNA without disturbing production of viral messenger RNA. Another primary field of interest is the study of events that lead to the assembly of viral nucleocapsids with viral matrix and envelope proteins at the sites of viral budding. Currently, we study the effect of microinjected antibodies made against synthetic peptides corresponding in sequence to the cytoplasmic, carboxy terminal portion of the vesicular stomatitis virus envelope protein.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02580-01 LMG

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Determinants of Virus-Host Cell Tropism

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

W. J. Bellini, Special Expert, Laboratory of Molecular Genetics, IRP, NINCDS

COOPERATING UNITS *(if any)*

Neuroimmunology Branch, NINCDS
Laboratory of Chemoprevention, NCI

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

Molecular Virology Section

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
4.7	4.2	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has as a final objective, the elucidation of those viral and host cell components which influence, at the molecular level, that phenomenon known as viral tropism. Currently, the emphasis of this project is focused on those components of measles virus which pertain to the neurotropism of this clinically relevant paramyxovirus.

During the course of natural infection, neurotropic variants of measles virus are generated. Frequently, this gives rise to mild central nervous system involvement and less frequently, to clinical encephalitis. In rare instances a delayed encephalitis, subacute sclerosing parencephalitis, is observed. Although the mechanism(s) of this neurotropism is unknown, available evidence suggests that the viral envelope glycoproteins are involved and can be antigenically distinguished from the wild type or vaccine strains using hybridoma antisera. Therefore, the initial phase of this project is to clone those genes encoding these proteins from a vaccine strain (Edmonston) of measles virus. From the nucleotide sequence, we will deduce the amino acid sequence of the proteins. To positively identify these clones, oligopeptides from the deduced amino acid sequence will be synthesized. Antisera raised against the synthetic peptides will then be used in a variety of immunologic techniques to identify the viral protein recognized and thus assign the clones. Once this is established, fragments of these cDNA clones will then be used as probes to identify their counterparts in neurotropic strains of measles virus presently available in our laboratory. The nucleotide and deduced amino acid sequence of the glycoproteins of the neurotropic strains will then be compared with the vaccine and wild type virus for regions of homology and non-homology.

The cloned glycoprotein genes will be placed in appropriate expression vectors to permit the study of their synthesis, regulation of expression, maturation and insertion into the host cell membrane.

PHS 6040 (Rev. 1/83) GPO 895-100

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02034-11 LMG

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Biology of Myelin-Forming Cells In Vitro and In Vivo

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Monique Dubois-Dalcq, M.D., Chief,
Section on Neural and Molecular Ultrastructure, LMG, IRP, NINCDS

COOPERATING UNITS *(if any)*

LDBA, NIDR; DMN, NINCDS; IDB, NINCDS; Department of Neuropathology, Albert Einstein College of Medicine; Department of Neurology, Johns Hopkins University School of Medicine.

LAB/BRANCH

Laboratory of Molecular Genetics

SECTION

Neural and Molecular Ultrastructure Section

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.7	2.5	1.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Myelin sheath allows fast saltatory conduction in PNS and CNS axons. This sheath is altered in diseases such as multiple sclerosis (CNS), Guillain-Barre and other neuropathies (PNS). Understanding how myelin is formed or repaired is crucial to the patient and requires basic studies of factors triggering differentiation of myelin-forming cells and their normal interaction with axons in vitro and in vivo. In the PNS, each Schwann cell makes a basement membrane before myelinating an axon. Although cultured rat Schwann cells do not synthesize myelin components in the absence of axons, they synthesize essential components of their basement membrane: laminin and collagen type IV. Laminin, a large glycoprotein, is secreted into the medium and binds to Schwann cell membrane, as seen with TEM. In addition, purified laminin promotes adhesion and elongation of Schwann cells and neurite outgrowth of sensory ganglia in a dose-dependent and specific manner. Thus laminin might play a role in Schwann cell-neuron interaction in development and regeneration at a stage preceding myelination. In contrast to Schwann cells, isolated oligodendrocytes synthesize in vitro myelin components such as galactocerebroside and basic protein (BP) while developing a phenotype resembling their in vivo counterpart. We are studying how and when BP is first synthesized by these cells and plan to use sensitive techniques of in situ hybridization to also detect BP transcripts. We will also investigate if the myelin-associated glycoprotein (MAG) is expressed in the absence of neurons. MAG is an integral membrane glycoprotein which is consistently associated with the periaxonal space, maintains the axon-Schwann cell contact (12-14 nm wide) and is not found in compact myelin (as seen by immunocytochemical techniques) in normal and pathological nerves in vivo. MAG has also been shown to be an antigen recognized by monoclonal IGM in paraproteinemia patients using electroblots. The antigenic site recognized appears to be the carbohydrate moieties of the molecule.

TAB 13 -- LABORATORY OF NEURAL CONTROL -- LNLC/IRP

ANNUAL REPORT

October 1, 1982 through September 30, 1983

Laboratory of Neural Control, Intramural Research Program
National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

Project Summaries:

Work on two projects, "Motor Control Systems in the Spinal Cord" and "Intrinsic Properties of Motor Units" has been especially unified during FY 1983. For the past several years, we have analyzed the morphology of group Ia muscle spindle afferents and the synaptic connections made by them on type-identified α-motoneurons in the cat spinal cord. Functionally identified afferents and motoneurons were injected intracellularly with horseradish peroxidase (HRP) and reconstructed from serial sections. Complete reconstructions have been made of 24 afferent-motoneuron contact systems, eight each for type FF, type FR and type S motoneurons. The 3-dimensional location of each synaptic contact has been tabulated in relation to the soma of the postsynaptic motoneuron. In addition, we now have completely reconstructed six α-motoneurons (two each of types FF, FR and S), specifying the position and dimensions of the cell soma and the 3-dimensional position of all dendritic segments, branch points and terminations, plus the lengths and diameters of all segments. This permits us to analyze, for the first time, the distribution of motoneuron membrane in space, as well as to compute the electrophysiological properties implied by the morphology of each motoneuron. The entire data base has been entered into computer files which have permitted an extensive series of analytic studies. Many of these utilize a newly-acquired Hewlett-Packard 9836 desktop computer with associated graphics accessories and computer programs developed by LNLC staff. Additional simulations and curve-fitting procedures have utilized the IBM 360 and DEC 10 computers in the NIH DCRT, as well as the NINCDS/NIMH VAX computer.

Previous work in LNLC, as well as in several other labs in Europe and Japan, suggested that the region within which synaptic contacts are established by Ia afferents on α-motoneurons is less extensive than that occupied by the entire motoneuron dendritic tree. Our new quantitative results show that Ia contacts are indeed relatively confined in the ventrolateral gray matter of the spinal cord to a roughly rectangular, box-like region centered on the target motoneuron somata and angled at about 45^{0} from dorsomedial to ventrolateral, following the trajectory of Ia afferent collaterals. Approximately 60 percent of the motoneuron surface lies within the Ia contact territory, irrespective of motor unit type. Furthermore, the spatial distribution of Ia contacts with distance from the motoneuron soma closely follows the curve of total membrane area with distance. This implies that group Ia contacts are arranged randomly on the motoneuron surface, depending only on the amount of membrane available at any given distance from the motoneuron soma. In addition, our results suggest that the average number of synapses made by individual Ia afferents on individual motoneurons is roughly the same, irrespective of motor unit type. These results provide new insight on several problems which arose in the past in the interpretation of electrophysiological characteristics of Ia synaptic potentials in α-motoneurons.

The data on reconstructed α-motoneurons has also permitted an analysis of the details of cell morphology. This has dealt in part with purely anatomical issues, such as the spatial distribution of dendritic segments and receptive membrane, one feature of which is noted above. In all cells studied, the dendritic tree is best described as radially arranged, although each cell shows some degree of asymmetry, particularly in the cross-section plane. Overall,

nowever, no consistent departure from radial symmetry is evident among triceps surae motoneurons, nor are there evident specializations of dendritic arrangment in motoneurons of different motor unit type. The results with the larger data base confirm conclusion reported in last year's Annual Report that the membrane area of α-motoneurons varies with motor unit type as follows: type FF > type FR > type S.

The last point relates to the most far-reaching feature of the present work, which has to do with our attempt to match the morphology of our motoneurons with the electrophysiological characteristics measured in the same cells before injection of HRP. Measurements of the input resistance (R_N), dendritic electrotonic length (L), and membrane time constant (τ_m) have been compared with estimates obtained from computer models based on the morphology of each motoneuron. This comparison depends primarily on the value(s) assumed for specific membrane resistivity (R_m) and the data available provide an approach to constraining the possible range of values for this critical factor. The data suggest that the overall R_m of type S motoneurons is systematically greater than that of type FR or FF cells (see Annual Report FY 1982). In addition, α-motoneurons cannot be represented as ideal membrane cylinders, as had been hoped in the past. Rather, their actual morphology introduces severe complications into the interpretation of electrophysiological data. Several aspects of these complications are being analyzed theoretically as well as by computer simulations based on actual neuronal morphology. The results to date suggest that R_m in α-motoneurons must be lower at and near than the cell soma and much higher in the dendrites, possibly by more than 100-fold in some fast twitch cells. The range of possible variation in the spatial distribution of R_m is being investigated by simulating membrane voltage transients in model neurons with the same dimensions as actual cells, and various assumed values for R_m. Comparison of these with voltage transients obtained experimentally should permit constraint on the ranges of R_m variation that are realistic. These findings have important implications for how neuronal dendrites process synaptic information. Additional modeling studies of synaptic potentials in realistic motoneuron models will be undertaken in FY 1984, when we have resolved the best estimates for the function(s) that govern the spatial distribution of R_m. Such simulations will use the anatomical data on spatial distribution of Ia contacts, discussed above.

The project entitled "Neuron Activity in Locomotion" has been renamed to "Neuromuscular Coordination of Movement", to reflect the evolution of projects subsumed under this title. A wide variety of techniques, both conventional and novel, are being used to study the motor performance of intact, behaving cats. The methods include: analysis of limb movements from videotape records of motor behaviors such as locomotion, scratching, jumping, postural adjustments, etc.; the use of multi-axis force plates to record force vectors applied to the supporting surface during motor performance; the use of chronically-implanted devices such as EMG electrodes, nerve cuff electrodes, semi-micro wire electrodes to record single afferent or motor axon firing patterns; and implanted tendon force and muscle length transducers. Many of these approaches and devices originated within LNLC, as detailed in previous Annual Reports. The motivating philosophy in this work is to utilize methods that permit obtaining information from intact, freely behaving animals in a form that enables interpretation according to the very large data base accumulated about the

behavior of neural elements in anesthetized, immobilized, or otherwise reduced preparations.

The major focus of the work in FY 1983 has been to study the mechanical architecture of appendages, including bones, joints and muscles, together with the dynamic patterns of activity in muscles and in the sensory receptor systems that are active during normal movements, in order to understand how the nervous system produces and controls coordinated movement. Attention in the past has focussed on the behavior of muscle spindle stretch receptors in order to infer the role of the fusimotor system in stereotyped and non-steroetyped movements. In addition, the implanted microwire electrode technique permitted, for the first time, reliable recording of the firing pattern of individual motoneurons during motor performance by intact cats. The results of these studies as applied particularly to multifunctional muscles, such as the hip flexor/knee extensor, sartorius, suggest that motoneurons and proprioceptive muscle afferents are organized into functional groups, or "task groups", which may or may not correspond to the anatomical segregations we recognize as "muscles". Cutaneous reflexes have been used as functional probes to examine: 1.) the qualitative polarity of effects on particular groups of motoneurons (e.g., whether they behave as "flexors" or "extensors" in flexion reflexes); and 2.) to delineate the modulation of reflex effects during various phases of repetitive movements such as stepping.

A new series of experiments has been started, applying the same approach to the study of the complex muscles that control head movement in the cat. These experiments, in collaboration with investigators at Queens University, Kingston, Canada, will permit further compartmentalization of motor functions within anatomically complex muscles. Preliminary experiments suggest that predictions made by the task-group hypothesis can explain some aspects of the motor performance of the complex neck muscles, which are extraordinarily rich in muscle spindle stretch receptor organs. The results to date suggest that segregation of motor and sensory elements into task groups permits optimization of the necessary neural control circuits to deal with relatively narrow ranges of kinematic muscle function. For example, the spring-like active lengthening that occurs in many antigravity extensors presumably requires quite different control systems that those that operate during ballistic contraction, or during fine isometric control of appendage position. The task group hypothesis suggests several avenues to test this prediction, which will be pursued in FY 1984.

Understanding the musculoskeletal system that is the organ of movement performance requires conceptual models of great complexity. In order to apply quantitative methods to these problems, model simulations that are firmly based on experimental data are most helpful. The project "Models of Neurophysiological Systems" (formerly titled "Models of Neural Interactions") applies methods of computer simulation to complex problems such as the influence of the fusimotor system on muscle spindle behavior during muscle actions that are actually observed during locomotion. With the data available from earlier work in LNLC, the predictions of one current model of spindle function have been compared with reasonable success to experimental results.

A problem growing out of this type of simulation concerns the influence of muscle architecture on the behavior of spindle afferents during normal movements, which depend not only on their muscle of origin but where they lie within that muscle. An analysis of the dynamic action of a structure such as the cat hindlimb in terms of motor control requires attention to such complexities in quantitative terms. To this end, we have initiated data collection and initial development of a computer-based dynamic model of the cat hindlimb, in collaboration with the Department of Electrical Engineering at the University of Maryland. The model ultimately will incorporate information about the skeletal framework, permissible joint angles, moments of inertia of limb segments, origins and insertions of muscles, and the internal fiber arrangements and fiber lengths within individual muscles. The model will then be updated with kinematic information about the muscle lengths, velocities, EMG signals, and, when possible, tendon forces during actions such as locomotion, together with force plate data about vertical and horizontal forces exerted on the ground. These data should permit prediction of activity patterns in particular muscles that would be required to produce observed movements and force patterns, which can then be matched against experimental observations. All these data can, in principle, be obtained during unrestricted, normal movements using chronic implant methods and videotape records of motor performance. The process of developing the hindlimb model has already suggested avenues of experimental investigation about the neural control networks necessary to produce observed outputs. It seems clear that further refinement will lead to increasingly sophisticated understanding of the neuromotor apparatus of the hindlimb of the cat, which has been a model system of choice for motor systems analysis for many years.

A new project entitled "Conduction Properties of Peripheral Nerve" was begun in FY 1983 to accommodate several subprojects that are related to existing projects in LNLC in that they utilize some chronic implant techniques. Methods have been evaluated to determine the best way to measure axonal conduction velocity in peripheral nerves in intact cats. Systematic study has shown that use of chronically-implanted, adjacent tripolar cuff electrodes with known interelectrode spacing, together with spike-triggered averaging, produces the most consistent results. The data obtained has already resolved a long-standing controversy about changes in conduction velocity in primary afferents from the periphery to dorsal roots (i.e., there is no significant slowing). This method is also being applied to study the effects of mechanical compression on the survival and regeneration of peripheral nerves. Compression is induced by surrounding the target nerve with Silastic tubes of known internal dimensions, in order to mimic such clinical conditions as median nerve compression syndrome. It is anticipated that this project will terminate in FY 1984.

Work on "Cortical Mechanisms of Voluntary Motor Control" has, during FY 1983, continued to examine the organization of motor output regions of the primate motor cortex during the performance of voluntary movement in awake monkeys. Methods have been developed to permit recording discharge patterns from individual neurons in the arm/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) during movement performance in minimally restrained, alert monkeys. Of particular recent interest is the influence of proprioceptive sensory input in modulating cortical cell activity. Brief

mechanical perturbations of the manipulandum gripped by the animal during flexion-extension task performance can induce changes in cortical cell firing at very short latency, implying transmission by oligosynaptic, rapidly conducting systems. The organization of effects is often analogous to those produced in spinal motoneurons by muscle spindle afferents and in such cases appear consistent with the much-debated notion of "long-loop reflexes" from proprioceptive afferents to motor cortex to spinal cord. The ability to examine the early effects of perturbations in forearm EMG signals has been enhanced in FY 1983 by the development of a new torque motor system with improved magnetic shielding.

One of the most interesting questions in motor control by the CNS has to do with the role of sensory feedback on movement performance. There is increasing evidence that some movement patterns (perhaps the vast majority) are emitted by the CNS as pre-programmed packages in which ongoing sensory feedback is not essential. Some of our observations are consistent with this notion, in that the discharge patterns of certain motor cortical cells become considerably less sensitive to modulation by sensory input during a phasic movement than when perturbations are introduced when the animal maintains a steady position. Interpretation of such findings is complicated because of the variety of possible sensory input systems that could participate, and the multiple levels at which sensory information can be controlled.

One approach to the analysis of the role of sensory feedback in movement performance is to examine CNS mechanisms related to hand-arm movement in the complete absence of sensory feedback. This can, in principle, be done by studying animals with complete uni- or bilateral deafferentation of the upper limb following surgical dorsal rhizotomy. Over the past two years, we have attempted to utilize a series of deafferented animals prepared at the Bronx Veterans Administration Hospital. The approach has been to train the animals to perform wrist flexion-extension tasks as used with normal monkeys, and to survey the appropriate regions of the motor cortex in order to compare the firing patterns of cortical cells with and without sensory feedback. Unfortunately, the deafferented animals were impossible to train satisfactorily. In addition, a number of technical setbacks ultimately made the project unfeasible. We are currently starting a pilot project in which normal animals will be trained on the relevant tasks before deafferentation surgery, to be done in LNLC. Having control of the entire process in LNLC should obviate the problems encountered with the donated monkeys.

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. For example, we have continued to evaluate various designs for a miniature Ta-Ta_2O_5 capacitor stimulating electrode, suitable for chronic implantation in the cortex or in deeper structures, 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 1983, we have begun the final assembly of a computer - microscope interface system, designed to facilitate collection of quantitative

data about neuronal morphology, as discussed above. A number of designs for this task have evolved elsewhere over the past 10 years, none of which is entirely satisfactory for the purposes envisioned in LNLC. After evaluating and inspecting several systems, some of which are very expensive, we have settled on a relatively simple design strategy based on the conventional camera lucida method. The mounting of transducers to measure microscope stage movement and fine focus, and the design and fabrication of interface devices between these and the computer, are almost complete. During FY 1984, we will complete the development of suitable software for collecting data, matching data sets from adjacent serial sections, and displaying complete reconstructions. In addition, we will evaluate a multi-contact, integrated circuit electrode system being fabricated elsewhere for suitability in recording unit activity in both motor cortex and spinal cord. The staff members involved in this project also continue to consult with other laboratories within NIH and in other institutions around the world on problems related to data collection and neural stimulation with chronic implant devices, in both clinical and research settings.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 01686-15 LNLC

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Motor Control Systems in the Spinal Cord

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Robert E. Burke, M.D. Chief, LNLC LNLC, NINCDS

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Neural Control

SECTION

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD 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 *(Use standard unreduced type. Do not exceed the space provided.)*

This project is designed to provide information on the mechanisms operating within reflex systems in the adult cat 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 interrelations between synaptic organization, intrinsic neuronal properties, and dynamic behavior of the alpha motoneurons, and the motor unit type, as defined by the physiological characteristics of the innervated muscle fibers. A variety of preparations have been used, including anesthetized, decerebrate animals as well as intact, freely moving cats. Electrophysiological and morphological data are obtained.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 01687-15 LNLC

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Techniques for Making Connections with the Nervous and Musculoskeletal Systems

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Martin J. Bak Electronics Engineer LNLC, NINCDS

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Neural Control

SECTION

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.8	0.2	1.6

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 01688-15 LNLC

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Cortical Mechanisms of Voluntary Motor Control

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Edward M. Schmidt, Ph.D. Biological Engineer LNLC, NINCDS

COOPERATING UNITS *(if any)*

Fundamental Neurosciences Branch, NINCDS

LAB/BRANCH

Laboratory of Neural Control

SECTION

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.4	0.9	1.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project is designed to investigate the size and spatial distribution of cortical neuron "colonies" in the primate motor cortex that are associated with individual muscles or closely related groups of muscles, as well as the activity of neurons in such colonies 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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02079-10 LNLC

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Models of Neurophysiological Systems

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)

William B. Marks, Ph.D.	Res. Physiologist	LNLC, NINCDS

COOPERATING UNITS *(if any)*

Electrical Engineering Dept.
University of Maryland

LAB/BRANCH
Laboratory of Neural Control

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.9	1.1	0.8

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

As quantitative data from a wide variety of techniques and levels of investigation become available for a particular nervous system function, it is both possible and advisable to attempt to assimilate such information into a comprehensive model of the underlying mechanisms and their interactions. This project consists of the development of such models and the necessary analytical and mathematical techniques for their implementation and testing in several areas of intensive experimental investigation by LNLC members and the scientific community at large.

A major collaborative effort with the University of Maryland was initiated this year to develop a comprehensive kinematic model of the cat hindlimb musculature during walking, and to use the intermediate results of applying existing data to such a model to guide the design and conduct of future experiments. The lengths and velocities of all significant hindlimb muscles during walking and other movements can now be obtained noninvasively. In the next year, this model will be extended to account for internal muscle fiber architecture and the effects of sarcomere length and velocity on tension output obtained for various levels of activation of hindlimb muscles. Eventually these various micro- and macroprocesses will be combined to generate a model which accurately reflects the individual characteristics of all the hindlimb muscles, which model will be used to test the validity of general theories and hypothetical principles of motor control. A new project has begun to model neurophysiologically realistic processes whereby a motor control network can formulate an output program to achieve a desired trajectory in a kinematically complex and redundant musculoskeletal system.

Efforts in previous years to model the processing of acoustic and electrical stimulation of the auditory nerve have resulted in two publications of models of these processes.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02080-10 LNLC

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neuromuscular Coordination of Movement

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Gerald E. Loeb, M.D. Medical Off., Research LNLC, NINCDS

COOPERATING UNITS *(if any)*

Dept. of Physiology
Queens Univ.
Kingston, Canada

LAB/BRANCH

Laboratory of Neural Control

SECTION

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.4	0.9	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The cat has long been a standard preparation for anatomical and acute physiological studies of muscle function and motor control at the spinal cord level. In this project, a wide variety of traditional and novel kinesiological techniques are being used to study the performance of motor tasks in unanesthetized, normally behaving cats. Techniques now in use include computer-aided reconstruction of skeletal movement from videotape, multi-axis force plates, and chronically implanted microelectrodes, nerve cuff and EMG electrodes, and strain and length transducers. The major focus has been the study of hindlimb muscles and their afferent and efferent control during walking, which is the subject of a computer modeling project described in Project No. Z01-NS-02079-10 LNLC. Other hindlimb movements studied include jumping, paw shaking, scratching, and reflexes to cutaneous nerve stimulation. A new study involves recording simultaneously from a large number of sites in the various neck muscles subserving head and scapular motion during normal movements such as eating, grooming, visual tracking, and locomotion.

The major objective is to correlate patterns of usage with the complex mechanics and compartmentalization and proprioceptive specializations of these muscles. A major theme emerging from these experiments is a concept of "Task Groups," which denotes the segregation and specialization of sensorimotor systems to perform kinematically homogeneous tasks in an optimal manner. In particular, it seems likely that groups of alpha and gamma motoneurons and related muscle spindles and their afferents are recruited specifically to perform kinematically well defined tasks. When a bifunctional muscle performs highly diverse tasks (e.g. active shortening vs. active lengthening), its pool of motor units is divided into independent groups which presumably employ different control programs optimized for each particular task.

Future work will ask how well these notions extend to other bifunctional muscles and will examine how much anatomical and physiological independence exists between task groups.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02160-09 LNLC

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Intrinsic Properties of Motor Units

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Robert E. Burke, M.D. Chief, LNLC LNLC, NINCDS

COOPERATING UNITS *(if any)*

Mathmatical Research Branch, NIADDK

LAB/BRANCH

Laboratory of Neural Control

SECTION

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.4	3.0	0.4

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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. Methods used include intracellular recording and stimulation, measurement of mechanical properties of muscles and individual muscle units, neuroanatomical techniques of intracellular staining with horseradish peroxidase, along with conventional and computer-aided methods for reconstruction of extensive neuronal structures from serial histological sections, and computer modeling and data processing. In some experiments, motor unit populations in normal animals are compared with those in animals after various conditioning treatments.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02534-01 LNLC

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Conduction Properties of Peripheral Nerve

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Gerald E. Loeb, M.D. Medical Off., Research LNLC, NINCDS

COOPERATING UNITS *(if any)*

Clinical Neurosciences Branch, NINCDS

LAB/BRANCH

Laboratory of Neural Control

SECTION

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.2	0.6	0.6

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project is concerned with the conduction of action potentials in peripheral nerve fibers in normal and damaged nerves. One study has been to develop and apply accurate methods for determining conduction velocity in short segments of peripheral nerves and spinal roots. This has resulted in the selection of spike-triggered averaging to obtain incremental latency in adjacent sets of tripolar nerve cuff electrodes, and the finding that there is no significant slowing of myelinated afferents from sciatic nerve to dorsal root in the cat.

A second study has been to apply this technique to the study of electrically evoked nerve potentials in chronically implanted animals during the periods of atrophy and regeneration in compressed peripheral nerves. This has permitted a detailed examination of the effects of and time course of recovery from experimentally induced neuropathy. Preliminary results suggest that the presence of a chronic constriction slows regeneration distally and that even after the distal segment has reached an almost normal conduction velocity, there may continue to be considerable slowing in the region of the constriction.

TAB 14 -- LABORATORY OF NEUROCHEMISTRY -- LNC/IRP

ANNUAL REPORT

October 1, 1982 to September 30, 1983

Laboratory of Neurochemistry

National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

ANNUAL REPORT
October 1, 1982 through September 30, 1983
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 Enzyme Chemistry 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

There are three main projects currently in progress in the Section on Cellular Neurochemistry.

a. Metabolic Profiles in Normal and Diseased Retina.

There are three specific studies being carried out at present. Cyclic GMP concentrations in the layers of the frog retina have been measured as a function of light, using a tungsten light source as well as fiber optics. Particular attention has been focussed on the changes during brief exposures to light (100 msec) in order to determine whether the cyclic nucleotide changes are rapid enough to consider this compound as a chemical transducer. It has become evident that a great deal of variability in cyclic nucleotides exists in dark-adapted retinas, and in retinas after brief exposure to light. The variability is considerably less after light exposures of 2 minutes or more. The variability is not confined to cyclic nucleotides, but appears to be true of metabolites such as 5' AMP and perhaps high-energy phosphate compounds. The significance of these findings is a subject of further investigation.

High-energy phosphate compounds are being measured in retinas of dogs bred to develop a progressive retinal dystrophy. The changes in biologically active compounds is being examined in 8 layers of the retina, in animals of varying ages and stages of the disease.

A new phosphodiesterase has been isolated from monkey and bovine retinas, which occurs in the interphotoreceptor matrix. The phosphodiesterases are responsible for the decreases in cyclic GMP in the photoreceptor which occur after light exposure. The significance of the various forms of phosphodiesterase in the compartments of the retina is being examined.

b. Coordinate Effects of Amphetamine on Brain Energy Metabolism and Protein Synthesis.

Two models of altered brain metabolism are being used to investigate changes in brain energy metabolism and protein synthesis, and the possible relationship of these two biological pathways. The inhibitory effect of amphetamine on brain protein synthesis has been shown to be due to the drug-induced hyperthermia. The drug effects on brain metabolism are not directly correlated with body temperature. It has thus been possible to dissociate the effects of amphetamine on protein synthesis and energy stores.

Studies have also been made on the effects of transient ischemia on metabolic events in gerbil brain. Energy stores are depleted within five minutes of ischemia, and are restored after minutes of reperfusion. Brain protein synthesis, however, remains depressed for several hours. The temporal coincidence of glycogen depletion and restoration with protein synthesis is being examined.

c. Metabolic Correlates of Neuronal Transmission in the Hippocampal Slice.

The relationship of energy status to synaptic events in the hippocampal slice preparation from guinea pig brain is being examined. High-energy phosphate stores have been increased by the addition of precursors, such as creatine, to the incubation medium. Subsequent stimulation of the slice under anoxic conditions demonstrated that increased energy stores prolonged the duration of the signal. These events suggest a relationship between energy status and synaptic transmission in tissue.

The loss of CA1 pyramidal neurons in the hippocampus of post-ischemic gerbils has now been well documented. The role of the creatine kinase system in these neurons is being examined with fluorescent antibody techniques. At the light microscope level, there is no observable deficit of creatine kinase prior to cell death, after which there is marked loss. Observations will be extended to the electron microscope level. These studies are being made to determine whether regions of high-energy demand are more sensitive to anoxic and/or ischemic insult.

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. From previous results, it is apparent that the restoration of the metabolic processes following an ischemic episode is more than a mere reversal of the events which occurred during ischemia. In addition, many events unique to the post-ischemic period increase in magnitude after longer ischemic episodes. The changes occurring during recirculation that are of particular interest include overshoots in glucose, glycogen and P-creatine as well as a decrease in glutamate and a large increase in cyclic AMP. It is increasingly evident that many of these changes result from the reoxygenation of an energy deficient tissue. However, some of the derangements may reflect an altered functional state of the brain during recirculation. A major effort is underway to investigate the underlying mechanisms involved in these apparently pathogenic events which occur during recirculation.

The demonstration that the CA1 neurons of the hippocampus die 4 days after 5 minutes of bilateral ischemia in the gerbil provides a useful model for the investigation of selective vulnerability of certain neurons to ischemia. Using microquantitative histochemistry, samples were dissected out from the CA1 and CA3 regions of the hippocampus as well as from the cerebral cortex. Metabolites from 4 different systems including glycolysis, the GABA shunt,

high-energy phosphates and the cyclic nucleotides were measured. In general, there are many delayed changes in the metabolites measured and the changes in the 3 regions are marked more by their similarities than their differences. This indicates that the recovery process extends for much longer periods of time than previously thought and further that effective post-ischemic therapy of stroke is a real possibility. There were some changes which may have some relevance to the eventual loss of the CA1 neurons. These include an elevation of cyclic GMP and a depression of cyclic AMP at 6 hours of recirculation in the CA1 region. In addition, the derangements in glutamate metabolism appeared to be more dramatic in the CA1 area than in the other two examined. Experiments are currently being performed to examine the fiber tracts, since the site of selective vulnerability may be located in the synaptic region, an area certainly more susceptible at least to pharmacological intervention.

Other models of ischemia are being used for specific purposes. The unilateral perfusion of the rat brain is a good model for transient ischemic accidents. Another advantage of this model is that the composition of the perfusate can be adjusted. For example, the metabolic response to anoxia at varying concentrations of glucose can readily be determined. The in vitro model of ischemia has been the basis for identifying the agonist responsible for the large post-ischemic rise in cyclic AMP. To date, the more common agonists of adenylate cyclase have been excluded and the emphasis now is on the prostaglandins.

b. Motor neuron diseases

Mice were infected with a neurotropic retrovirus (Lake Casitas strain) and various metabolites were examined in the cerebellum, cerebral cortex and spinal cord of affected (paralyzed) and unaffected mice. In the affected mice, the levels of the cyclic nucleotides, high-energy phosphates and glycogen were altered in the spinal cords of affected mice. The concentrations of these metabolites are being determined at various stages following inoculation.

c. Experimental seizures

The hippocampus slice is a very good system to study the relationship between brain function and the energy status of the tissue. It has been demonstrated that the energy reserves of the brain slice can be elevated by adding creatine to the medium. The nature of the evoked potential at various high-energy phosphate concentrations of the slice is currently being investigated.

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 is known that transplantation antigens are responsible for allograft rejection, and in accordance with this, previous work has shown that normal

(untreated) rats reject nerve allografts. On the other hand, treatment of rats with the immunosuppressive agent Cyclosporin-A (CyA) prevents them from rejecting nerve with the consequence that host axons can regenerate through a long length (4 cm or more) of nerve allograft. Current results with CyA revealed that short-term treatment (2-5 weeks) with this agent did not induce tolerance to nerve as has been reported for heart and kidney allografts. In addition, CyA inhibited rejection indefinitely in sensitized recipients. Pretreatment of a nerve allograft with irradiation sufficient to destroy allogeneic leukocytes (one source of the immunogenic stimulus) did not prevent nerve rejection. An analysis of the basement membrane (using antibody to its specific components, e.g., laminin) of rejected allogeneic Schwann cells demonstrated that this structure persisted as a shrunken and deformed tube which, by itself, did not act as a conduit for regenerating host axons. Future studies will be directed toward identifying and removing or altering the immunogenic component of a nerve allograft. In this way it may be possible, without or with immunosuppression, to induce tolerance to allogeneic nerve grafts.

b. Neurotrophic studies

This series of experiments is concerned with the role of extracellular matrix (ECM) in regeneration and trophic interactions of nerve and target cells. Antibodies to specific macromolecular components of basement membrane (BM) were used to monitor changes in BM of regenerating muscle and nerve induced by autotransplantation. We found that BM was degraded of certain components (fibronectin, laminin, and type IV collagen) in a sequential manner. Although anatomical studies have shown BM degradation, our results revealed a biochemical sequence. It is possible that sequential BM degradation is a signal for myosatellite and Schwann cell proliferation which prepares these two different tissues for regeneration. A study of limb regeneration after amputation in the newt demonstrated that the ECM component fibronectin accumulated during blastemal growth and early tissue differentiation and disappeared as maturation of leg tissue (e.g., cartilage, muscle) evolved. Our goal is to determine the specific role of ECM components in regeneration and use this knowledge to promote tissue repair.

Section on Enzyme Chemistry

The research program of the Section on Enzyme Chemistry is designed to obtain a detailed description of the structure of the Na,K-ATPase and of the molecular events that produce active transport of sodium ions.

a. Transient kinetics

One part of this project involves the use of the rapid quenching technique for the measurement of pre-steady-state kinetics of the phosphorylation and dephosphorylation of the Na,K-ATPase. The apparatus used permits two-stage addition of reagents so that kinetics of reaction intermediates that are not directly accessible to analysis can be indirectly measured by effects on the pseudo-steady-state levels of phosphoenzyme and rates of phosphate release. From measurements of the transient kinetics of phosphorylation of Na,K-ATPase they have shown that the functional enzyme may be a dimer which can display half-of-sites reactivity.

b. Multiple forms of Na,K-ATPase

A second objective of this project is to investigate the evidence for multiple forms of Na,K-ATPase in brain and other tissues. The section has obtained evidence that some of the variation in cardiac glycoside sensitivity which has been used to characterize different forms of the ATPase can be due to differences in the membrane in which the enzyme is inserted. Several new techniques for assessing minor differences in the structure of closely related forms of the ATPase are under development.

c. Structure and regulation of sodium pump in brain

A third phase of this investigation is concerned with the solubilization and purification of brain Na,K-ATPase. By employing a new detergent, Albers and co-workers have achieved nearly quantitative solubilization of the brain Na,K-ATPase. Molecular-sieving studies indicate that the soluble form must be an oligomer of higher molecular weight than previously obtained.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02256-07 LNC

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Metabolic Profiles in Normal and Diseased Retina

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Janet V. Passonneau, Chief, Laboratory of Neurochemistry, NINCDS

COOPERATING UNITS *(if any)*

Laboratory of Vision Research, NEI
University of Pennsylvania School of Veterinary Medicine

LAB/BRANCH

Laboratory of Neurochemistry, IRP, NINCDS

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 *(Use standard unreduced type. Do not exceed the space provided.)*

Three studies on retina are in progress. cGMP levels have been measured in the layers of frog retina as a function of light, using both a tungsten lamp and fiber optics as light sources, and times ranging from 0.1 sec to 2 hours of light. There was a drop in cGMP by 0.1 sec followed by further and larger drops at 2 sec and 2 min. In addition, there was a high level of variability in both dark animals as well as those exposed to short periods (0.1, 1 and 2 sec) of light. This variability disappeared after longer (2 minute) exposures.

High energy phosphate compounds are being measured in retinas of dogs bred to develop a progressive retinal dystrophy. Eyes from controls, carriers and diseased animals of varying chronological age are sectioned, freeze-dried, and the retinas dissected into 8 layers plus tapetum. They are then analyzed by the oil-well technique for ATP plus ADP to see if there are changes in metabolite levels with either age or disease.

A new phosphodiesterase has been isolated from monkey and bovine retinas. It is in high concentration in the interphotoreceptor matrix between outer segments and pigment epithelial processes. It has a subunit M_r=43 K but has a high M_r native configuration. The K_m for cGMP is about 35 uM while that for cAMP is 2.3 mM. It occurs tightly bound to an inhibitory protein which is heat stable.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02455-03 LNC

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Metabolic Correlates of Neuronal Transmission in the Hippocampal Slice

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Janet V. Passonneau, Chief, Laboratory of Neurochemistry, NINCDS

COOPERATING UNITS *(if any)*
None

LAB/BRANCH
Laboratory of Neurochemistry, IRP, NINCDS

SECTION
Section of 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 *(Use standard unreduced type. Do not exceed the space provided.)*

The role of the creatine kinase system in maintaining neuronal function is being studied in the hippocampus. Antibody to the BB isozyme of creatine kinase is applied to control and post-ischemic gerbil brains to determine if a loss in neuronal content of this enzyme leads to the death of CA1 pyramidal cells at 3-4 days post-ischemia. At the light microscope level there has been no observable deficit prior to neuronal degeneration. Loss of the CA1 cells did result in marked loss of antibody labeling in the CA1 region of the anterior hippocampus. These observations are being extended to the electron microscope level. The staining pattern may indicate areas of high energy demand which would be expected to show the greatest sensitivity to ischemia or anoxia. A comparison is being made of the rates of change in high energy phosphate (ATP and PCr) concentrations during anoxia and ischemia in vitro. The results should indicate the relative importance of anaerobic glycolysis in maintaining synaptic transmission during anoxia in the hippocampal slice. While ischemia appears to cause a more rapid fall in slice ATP levels, it is not clear that the evoked electrophysiological response is abolished more rapidly under these conditions compared to anoxia. Several electrophysiological parameters are being studied in hippocampal slices prepared from gerbils before or for 4 days following 5 min bilateral ischemia. The results fail to show any significant difference between CA1 cells in the anterior hippocampus, which die within 4 days, and those which survive in the lateral hippocampus.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02429-04 LNC

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Coordinate Effects of Amphetamine on Brain Energy Metabolism and Protein Synthesis

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Janet V. Passonneau, Chief, LNC, NINCDS

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Neurochemistry, IRP, NINCDS

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 *(Use standard unreduced type. Do not exceed the space provided.)*

Coordinate changes in brain energy metabolism and protein synthesis are investigated using two models of altered brain metabolism -- amphetamine hyperthermia in mice, and transient ischemia in gerbils. Protein synthesis status is determined using an in vitro amino acid incorporation method which provides information analoguns to polyribosome profiles. Glycogen, glucose, phosphocreatine, adenine and guanine nucleotides and other metabolites are measured enzymatically.

Previous studies in this laboratory have demonstrated that the inhibition of protein synthesis by amphetamine is a consequence of drug-induced hyperthermia, inhibition occurring abruptly between 40 and 41°C. Protein synthesis is affected in liver and kidney as well as brain, and the same effect is produced directly by warming the animals at 42°C. Brain glycogenolysis following amphetamine administration is more pronounced in hyperthermic animals, but does not correlate well with temperatures of individual mice. Other measures of energy status are not significantly affected. The reduction in brain protein synthesis is thus dissociated from effects on known components of energy metabolism.

During transient ischemia in gerbils, brain metabolism is drastically altered, ATP, PCr and GTP being totally depleted. Within minutes of reperfusion, most measures of energy status have returned to control levels, while brain protein synthesis remains depressed for several hours. Of the several metabolites measured, we have found that only glycogen shows a delayed recovery comparable to that observed for protein synthesis. While a link between protein and glycogen metabolism remains to be established, this model holds considerable promise as an experimental system in which to investigate metabolic regulation of brain protein synthesis.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02142-09 LNC

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Cerebral Metabolism in Altered Metabolic States of the CNS

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
W. David Lust, Head, Section on Neurochemistry Pharmacology, LNC, IRP, NINCDS

COOPERATING UNITS *(if any)*
Department of Neurology, Johns Hopkins School of Medicine, Baltimore, Maryland

LAB/BRANCH
Laboratory of Neurochemistry, IRP, NINCDS

SECTION
Section on Neurochemical Pharmacology

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.1	0.7	1.4

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The CA 1 neurons of the hippocampus have been shown to disappear by 4 days after 5 minutes of bilateral ischemia in the gerbil brain. The selective vulnerability of these neurons to short periods of ischemia provides an excellent model for the examination of the neurochemical events which precede neuronal death. In the initial study, metabolites were measured in the cell body layer of the CA 1 and CA 3 region of the hippocampus as well as in the cerebral cortex. The metabolites selected for measurement were associated with 1) energy metabolism, 2) glycolysis, 3) the GABA shunt and 4) synaptic transmission (i.e., cyclic nucleotides). The energy status, as reflected by the levels of ATP and P-creatine, was maintained from 1.5 to 48 hours of recirculation after which there was a drop but only in the affected region. The levels of glycogen and glucose were elevated during the early stages of recirculation , whereas those for lactate were somewhat depressed. These changes collectively suggest that there is a period of hypometabolism in all regions for up to 1 day of recirculation. By four days of recirculation, the glycolytic metabolites were significantly elevated but only in the CA 1 region which undoubtedly reflects the glial infiltration which occurs with the loss of the neurons. The levels of both GABA and glutamate decrease to varying degrees during recirculation, but as with the other metabolites the changes in the three regions are marked more by their similarities than their differences. Under normal circumstances, it is generally conceded that the metabolic rate of the brain is coupled to brain function; however, in various neurological disorders it is possible that the functional status of the brain may be influenced by the perturbations in metabolism like those which occur during recirculation. The changes in GABA and glutamate provide some support for this possibility, since both are constituents of a major metabolic pathway and also serve as neurotransmitters. In addition, the delayed changes in the metabolites indicate that an effective post-traumatic treatment of stroke is a real possibility.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02257-07 LNC

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neuropharmacology of Cerebral Metabolism

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

W. David Lust, Head, Section on Neurochemical Pharmacology, LNC, IRP, NINCDS

COOPERATING UNITS *(if any)*

Pharmacology Laboratory, Epilepsy Branch, CDNDP, NINCDS

LAB/BRANCH

Laboratory of Neurochemistry, IRP, NINCDS

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 *(Use standard unreduced type. Do not exceed the space provided.)*

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 was added to the incubation medium for varying periods of time and the accumulation of P-creatine and ATP were determined. While the levels of ATP did not change over a 5 hour incubation, the concentration of P-creatine increased by 4- and 6-fold at 3 and 5 hours of incubation, respectively. The perforant pathway axons were stimulated and the activity recorded in the region of the dentate gyrus. The loss of the signal during anoxia was delayed in those slices incubated with creatine which suggests a relationship between synaptic transmission and energy status of the tissue. In certain neurological disorders, enlarging the energy reserves of the brain might prevent or minimize the deficits induced by the insults. However, attempts to elevate P-creatine by injection of creatine into the ventricles of the brain have generally failed. Therefore, the characteristics of the creatine-induced increase in P-creatine in brain slices is being examined. Preliminary data suggest that the availability of phosphate may be important to the generation of P-creatine.

Naloxone has been shown to reverse many of the behavioral effects resulting from brain ischemia. The level of analgesia was determined in bilaterally ischemia gerbils and found to be significantly higher than in control gerbils. This effect was reversed by the administration of 1 mg/kg (ip) of naloxone. In addition, the stereotypical behavior during ischemia was partially prevented. In spite of these changes, one criterion of ischemic injury, namely the loss of CA 1 neurons by 4 days of recirculation after 5 minutes of bilateral ischemia, was not altered by naloxone pretreatment. Studies including the measurement of endogenous opiates are underway to determine the nature of the naloxone effect.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 01586-16 LNC

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Trophic Interactions of Neurons and Target Cells

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Andrew A. Zalewski, Section Chief, Laboratory of Neurochemistry, IRP, NINCDS

COOPERATING UNITS *(if any)*
Mineralized Tissue Research Branch, NIDR

LAB/BRANCH
Laboratory of Neurochemistry, IRP, NINCDS

SECTION
Section on Neuronal Development and Regeneration

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.60	0.40	0.20

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The growth and differentiation of target tissue can be influenced by trophic agents and extracellular matrix (ECM) components. A series of studies are planned to investigate the role of ECM in regeneration in vivo of muscle, nerve, limb, and taste buds. Antibodies to the ECM macromolecules fibronectin, laminin, and type IV collagen were used to monitor changes in ECM by an indirect immunofluorescent technique. We were particularly interested in changes in basement membrane (BM) since this structure is thought to act as a tube within which muscle and nerve fiber regeneration occurs. We found that the BM of myofibers and Schwann cells was sequentially degraded of its components. Fibronectin was lost first; laminin and type IV collagen disappeared later but at about same time. Although it is known from anatomical studies that BM is degraded, our results demonstrated a biochemical sequence. It is conceivable that the sequential degradation of BM is a signal for myosatellite and Schwann cell proliferation which prepares muscle and nerve for regeneration. In a study of limb regeneration, fibronectin was examined since this ECM glycoprotein is involved in cell-to-cell adhesion, cell-to-substratum binding, and cell migration. After limb amputation in newts, increased amounts of fibronectin appeared throughout the ECM of the undifferentiated blastemal cells and persisted during blastemal growth and early stages of redifferentiation of limb tissues (e.g., cartilage, muscle). As limb tissue matured, most of the ECM fibronectin disappeared. These results showed that fibronectin changed in ECM during the dedifferentiation and redifferentiation of tissues in regenerating newt limb. Our goals are to determine the specific role of ECM components in regeneration and to use this knowledge to promote tissue repair.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02254-07 LNC

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Repair of injured nerve with a nerve allograft

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)

Andrew A. Zalewski, Section Chief, Laboratory of Neurochemistry, NINCDS

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Neurochemistry, IRP, NINCDS

SECTION

Section on Neuronal Development and Regeneration

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.40	1.60	0.80

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Cyclosporin-A (CyA) treatment of rats prevents them from rejecting nerve allografts. The purpose of this project is to evaluate factors which might contribute to the use of nerve allografts and CyA to aid in the repair of injured nerve. Studies were performed to determine (1) whether short-term courses of CyA induce tolerance, (2) the effectiveness of CyA in preventing rejection in sensitized hosts, (3) whether allograft treatment before transplantation (e.g., irradiation) alters its immunogenicity, and (4) the role of Schwann cell basement membrane in axonal regeneration. Inbred strains of rats were used. Our results demonstrated that, in contrast to heart and kidney, short-term courses (2-4 weeks) of CyA did not induce tolerance to nerve allografts regardless of whether the allograft contained major and minor or only minor transplantation antigens. In addition, CyA was found to indefinitely prevent the rejection of nerve allografts in sensitized hosts. We tried to reduce the immunogenicity of nerve allografts by irradiating them prior to transplantation. A dose of 1000 Rads, which should be lethal to intravascular and interstitial grafts leukocytes (i.e., one source of the immunogenic stimulus) but not Schwann or vascular cells, was used. We found that irradiation of a nerve allograft did not prevent its rejection. An analysis of the basement membrane (using specific antibody to its components, e.g., laminin), of rejected allogeneic Schwann cells revealed that this structure persisted as a shrunken and deformed tube which, by itself, did not act as a conduit for regenerating host axons. Future studies will be directed toward identifying the cell or cell-types in a nerve allograft which provoke the immune reaction. If this can be accomplished it might be possible to eliminate this immunogenic source from the allograft and promote its permanent acceptance with short-term immunosuppression.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 00813-22 LNC

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Enzymological Aspects of Neural Functions

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
R. W. Albers, Chief, Section on Enzyme Chemistry, LNC, IRP, NINCDS

COOPERATING UNITS *(if any)*
Laboratory of Molecular Aging, NIA

LAB/BRANCH
Laboratory of Neurochemistry, IRP, NINCDS

SECTION
Enzyme Chemistry

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.5	2	1.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project is a study of the molecular bases of the active transport of Na^+ and K^+. The mechanism of the Na, K-ATPase has been investigated using a rapid mixing technique for measuring the transient kinetics of its phosphorylation by ATP and subsequent dephosphorylation. We have shown that the manner in which oligomycin interacts with the enzyme provides evidence that the sodium pump functions as a dimer: under certain conditions only half of the subunits bind oligomycin.

Regulation of sodium pump activity in brain is currently under study. We have developed rapid methods for measuring and analysing the kinetics of ouabain inhibition of the Na,K-ATPase. This method has allowed us to detect multiple forms of the sodium pump in brain membranes.

A method for quantitatively extracting the Na,K-ATPase from brain in soluble form has been developed. Molecular sieving studies indicate that this soluble form is a monodisperse component with an apparent molecular weight of about 1000 KDa.

Current and future studies are directed at attempting to obtain a physical separation of the two major forms of Na,K-ATPase in brain and in further exploration of possible mechanisms which may regulate their levels of activity.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02254-07 LNC

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Repair of injured nerve with a nerve allograft

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Andrew A. Zalewski, Section Chief, Laboratory of Neurochemistry, NINCDS

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Neurochemistry, IRP, NINCDS

SECTION

Section on Neuronal Development and Regeneration

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.40	1.60	0.80

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Cyclosporin-A (CyA) treatment of rats prevents them from rejecting nerve allografts. The purpose of this project is to evaluate factors which might contribute to the use of nerve allografts and CyA to aid in the repair of injured nerve. Studies were performed to determine (1) whether short-term courses of CyA induce tolerance, (2) the effectiveness of CyA in preventing rejection in sensitized hosts, (3) whether allograft treatment before transplantation (e.g., irradiation) alters its immunogenicity, and (4) the role of Schwann cell basement membrane in axonal regeneration. Inbred strains of rats were used. Our results demonstrated that, in contrast to heart and kidney, short-term courses (2-4 weeks) of CyA did not induce tolerance to nerve allografts regardless of whether the allograft contained major and minor or only minor transplantation antigens. In addition, CyA was found to indefinitely prevent the rejection of nerve allografts in sensitized hosts. We tried to reduce the immunogenicity of nerve allografts by irradiating them prior to transplantation. A dose of 1000 Rads, which should be lethal to intravascular and interstitial grafts leukocytes (i.e., one source of the immunogenic stimulus) but not Schwann or vascular cells, was used. We found that irradiation of a nerve allograft did not prevent its rejection. An analysis of the basement membrane (using specific antibody to its components, e.g., laminin), of rejected allogeneic Schwann cells revealed that this structure persisted as a shrunken and deformed tube which, by itself, did not act as a conduit for regenerating host axons. Future studies will be directed toward identifying the cell or cell-types in a nerve allograft which provoke the immune reaction. If this can be accomplished it might be possible to eliminate this immunogenic source from the allograft and promote its permanent acceptance with short-term immunosuppression.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 00813-22 LNC

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Enzymological Aspects of Neural Functions

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
R. W. Albers, Chief, Section on Enzyme Chemistry, LNC, IRP, NINCDS

COOPERATING UNITS *(if any)*
Laboratory of Molecular Aging, NIA

LAB/BRANCH
Laboratory of Neurochemistry, IRP, NINCDS

SECTION
Enzyme Chemistry

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.5	2	1.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project is a study of the molecular bases of the active transport of Na^+ and K^+. The mechanism of the Na, K-ATPase has been investigated using a rapid mixing technique for measuring the transient kinetics of its phosphorylation by ATP and subsequent dephosphorylation. We have shown that the manner in which oligomycin interacts with the enzyme provides evidence that the sodium pump functions as a dimer: under certain conditions only half of the subunits bind oligomycin.

Regulation of sodium pump activity in brain is currently under study. We have developed rapid methods for measuring and analysing the kinetics of ouabain inhibition of the Na,K-ATPase. This method has allowed us to detect multiple forms of the sodium pump in brain membranes.

A method for quantitatively extracting the Na,K-ATPase from brain in soluble form has been developed. Molecular sieving studies indicate that this soluble form is a monodisperse component with an apparent molecular weight of about 1000 KDa.

Current and future studies are directed at attempting to obtain a physical separation of the two major forms of Na,K-ATPase in brain and in further exploration of possible mechanisms which may regulate their levels of activity.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02430-04 LNC

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Aspects of Calcium Metabolism in Electric Tissue

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

R. Wayne Albers, Head, Section on Enzyme Chemistry, LNC, IRP, NINCDS

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Neurochemistry, IRP, NINCDS

SECTION

Section on Enzyme Chemistry

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 *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been terminated.

ANNUAL REPORT

October 1, 1982 through September 30, 1983

Laboratory of Neuro-otolaryngology
National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

ANNUAL REPORT
October 1, 1982 through September 30, 1983
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 to provide new knowledge within the framework of its two Projects: Project Number Z01NS02216-08 LNO, Inner Ear Neuronal Mechanisms: A Multidisciplinary Analysis, Project Number Z01NS02217-08 LNO, Synaptic Transmission and Neuronal Connections of the Mammalian Cochlear Nucleus. Through these Projects we aim at a better understanding of how the inner ear can make us hear and how the cochlear nucleus processes the auditory information that it receives from the inner ear.

We share with many others the working hypothesis that the system of efferent neurons impinging on outer hair cells of the organ of hearing may influence the degree to which outer hair cells may control inner hair cell excitation, which in its turn may decide how we hear. This year we have published a biochemical study indicating that efferent neurons in the cochlea contain at least two different opioid peptides. Having refined our techniques, and concentrating on the auditory sensory organ of the cochlea, we have a study in progress with findings indicating there are at least three such peptides in the sensory organ. We are now trying to specify the nature of an opioid peptide in the efferents impinging on outer hair cells, through a combination of techniques involving partial denervation of the cochlear efferents and biochemical determinations, using high performance liquid chromatography (HPLC) and radioimmunoassay (RIA). Using immunocytochemical techniques, we have also shown that the efferents to the outer hair cells contain choline acetyltransferase-like immunoreactivity, strengthening previous evidence that these efferents are cholinergic. We are planning an electron microscopical study of the outer hair cells to try to define structural changes elicited by stimulation of hair cell receptors at efferent synapses.

As a complement to the study of the cochlear efferents in the cochlea we have a study in press on the co-containment of enkephalin-like immunoreactivity and acetylcholinesterase-activity in brainstem cells of origin of cochlear efferents. Also, a study is in progress of a corresponding co-containment of enkephalin-like immunoreactivity and choline acetyltransferase-like immunoreactivity.

For technical reasons our studies on opioid peptides have also this year been extended to the hippocampus and the retina. One paper is in press, describing findings in the hippocampus of three different enkephalin-like peptides with the use of biochemical techniques and showing the distribution in the hippocampus of enkephalin-like immunoreactivity using immunocytochemical means for visualization; a biochemical study of the retina is being submitted for publication.

In our continued studies of the immunocytochemical localization of neurotransmitter candidates and enzymes in the organ of hearing we have found

no reliable clue regarding the nature of the neurotransmitter(s) that the sensory cells may use. We will continue such studies, also looking for specific markers of inner and outer hair cells.

We have published a study on the postnatal development of the spiral ganglion cells of the auditory nerve in the rat cochlea, as observed under the light microscope and electron microscope. A study is in progress on the development of glutaminase-like and aspartate aminotransferase-like immunoreactivity of spiral ganglion cells. These and related studies are carried out in an attempt to find markers as means of differentiating between the two kinds of spiral ganglion cells, between the dendrites of spiral ganglion cells at the hair cells in the auditory sensory organ and between the synaptic projections of the two types of spiral ganglion cells in the cochlear nucleus.

Our studies of auditory nerve synapses in the cochlear nucleus, described in previous Annual Reports, gave rise to our hypothesis that the enzymes aspartate aminotransferase and glutaminase may serve as markers for neurons using glutamate and/or aspartate as neurotransmitter(s). To find evidence for or against this hypothesis, we are pursuing our immunocytochemical studies of the distribution of these enzymes in the nervous system. Two papers have previously been published, on aspartate aminotransferase-like immunoreactivity in the cochlear nucleus respectively in the retina. One paper on glutaminase in the auditory nerve has now been submitted for publication and several manuscripts on both enzymes are in preparation.

Previously reported electron microscopical studies of the development of auditory nerve synapses in the cochlear nucleus of the rat have been completed and have led to the publication of three papers.

The use of brainstem slices for the physiological and pharmacological study of auditory nerve synapses has continued with drugs applied to the bath of the slice chamber and through microiontophoresis. Slices containing the hippocampus of the mouse have been used as control preparations for testing the parameters of the experiments. Such control experiments have led to interesting findings on potentiation in the hippocampus: the results are being submitted for publication. Manuscripts on the cochlear nucleus auditory nerve synapses are in preparation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01NS02216-08 LNO

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Inner ear neuronal mechanisms: a multidisciplinary analysis

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Jörgen Fex, Chief, Laboratory of Neuro-otolaryngology, NINCDS

COOPERATING UNITS *(if any)* Lab. of Neuropathology & Neuroanatomical Sciences, NINCDS
Dept. Psychobiology, University of California, Irvine, CA
Max Planck Inst. für Psychiatrie, Abteilung f.Neurochemie, Martinsried, Germany

LAB/BRANCH

Laboratory of Neuro-otolaryngology

SECTION

INSTITUTE AND LOCATION

NINCDS, NIH, BETHESDA, MARYLAND 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
6.8	4.5	2.3

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is to provide new knowledge of the auditory mechanisms of the inner ear.

We have continued our studies on the immunocytochemical localization of neurotransmitter candidates and enzymes in the auditory sensory organ. Small mammals (guinea pigs, rats and mice) served as research subjects. Antisera to choline acetyltransferase, aspartate aminotransferase, glutaminase and enkephalins have given positive antigen-antibody reactions. Negative findings have resulted from the use of antisera to substance P, ACTH, LHRH, alpha MSH, neurotensin and somatostatin. The results have given no reliable clue regarding the nature of the neurotransmitter(s) that the hair cells of the auditory sensory organ may use. On the other hand, the case for the cholinergic nature of efferent, olivocochlear fibers has been strengthened: we have found choline acetyltransferase-like immunoreactivity in synaptic regions under both inner and outer hair cells. Also, ongoing biochemical studies indicate there are at least three opioid peptides in the auditory sensory organ of the guinea pig. We now have also demonstrated co-containment of enkephalin-like immunoreactivity and acetylcholinesterase in brainstem cells of origin of a subpopulation of the cochlear efferents of the guinea pig, using immunocytochemical and histochemical techniques and light microscopy.

We believe with many that synaptic activity of efferents at outer hair cells changes the micromechanics of the auditory sensory organ. We will try to find out how, if at all, such activity may change the microstructure of the outer hair cell.

We continue to look for markers of the different parts of the two types of spiral ganglion cells of the auditory nerve. For this reason, and others, we have studied the postnatal development of the spiral ganglion cells of the rat. A study is in progress on the development of glutaminase-like and aspartate aminotransferase-like immunoreactivity of spiral ganglion cells.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01NS02217-08 LNO

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Synaptic transmission and neuronal connections of the mammalian cochlear nucleus

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Jörgen Fex, Chief, Laboratory of Neuro-otolaryngology, NINCDS

COOPERATING UNITS *(if any)* Lab. of Neurophysiology, NIMH; Dept. Psychobiology, Univ. of Calif., Irvine, CA; Dept. of Biochemistry, Univ. of Pittsburgh, Pittsburgh, PA; Dept. of Neurobiol., SUNY, Stony Brook, NY; Dept. of Neurophysiology, Univ. of Wisconsin, Madison, WI

LAB/BRANCH
Laboratory of Neuro-otolaryngology

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.8	1.5	2.3

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is to provide new knowledge of how the cochlear nucleus processes the auditory information that it receives from the inner ear through the auditory nerve.

We have in previous reports described findings indicating that the auditory nerve may use glutamate and/or aspartate as neurotransmitter in the cochlear nucleus. A logical outcome of these studies is our hypothesis that the enzymes glutaminase and aspartate aminotransferase may serve as markers for neurons that have glutamate and/or aspartate as neurotransmitter(s). To find evidence for or against this hypothesis and to get a better perspective of our findings on auditory nerve synapses we are pursuing immunocytochemical studies of the distribution of these enzymes in different parts of the nervous system. Small mammals (guinea pigs and rats) serve as research subjects; immunocytochemical techniques, light microscopy and electron microscopy are used. One paper on glutaminase in the auditory nerve has been submitted for publication; several manuscripts on both enzymes are in preparation.

Previously mentioned electron microscopical studies of the development of auditory nerve synapses in the cochlear nucleus of the rat have been completed and have led to the publication of three papers.

Our in vitro studies of auditory nerve synapses in the cochlear nucleus have been continued. Chamber mounted slices of the brainstem of mice have been prepared, drugs have been applied to synapses, either via fluid in the chamber as bath application, or through microiontophoresis. Slices containing the hippocampus of the mouse have been used for testing the parameters of the experiments. Such control experiments have led to interesting findings on potentiation in the hippocampus; results are being submitted for publication. Manuscripts on auditory nerve synapses are in preparation.

ANNUAL REPORT

October 1, 1982 through September 30, 1983

Laboratory of Neuropathology and Neuroanatomical Sciences
National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

Table of Contents (cont'd)

Table of Contents (cont'd)

ANNUAL REPORT
October 1, 1982 through September 30, 1983
Laboratory of Neuropathology and Neuroanatomical Sciences, IRP
National Institute of Neurological and Communicative Disorders and Stroke

Igor Klatzo, Chief

During the past year, the LNNS has marked a significant progress in several research areas:

The Section on Cerebrovascular Pathology has elucidated further the pathophysiology of the blood-brain barrier (BBB) in cerebral ischemia. Following demonstration of two independent BBB openings to proteins occurring after release of arterial occlusions, our studies have been directed toward elucidation of the mechanisms involved. Thus, it has been established that the final opening of the barrier follows a severe ischemia (cerebral blood flow [CBF] 12 ml/100 g/min) resulting in marked reactive hyperemia (CBF elevated 100-300% over the pre-isehcmic values) in the previously ischemic regions in which the vessels lose their autoregulation. The second opening of the barrier, occurring after a refractory period, was correlated with severe ischemic damage to the tissue causing release of some compounds which stimulate the barrier opening. Our studies demonstrated that, by inducing hypovolemia by withdrawing blood at the time of recirculation, the reactive hyperemia can be prevented, as well as the first opening of the BBB. Furthermore, our studies demonstrated that prevention of the BBB breakdown and extravasation of serum proteins by hypovolemia results in a considerable reduction of edema in the ischemically affected regions, when compared with normovolemic animals which suffered ischemia of similar intensity.

In another study, effect of serum protein extravasation on water content of the brain tissue was evaluated in an experimental model in which breakdown of the BBB to proteins was produced without evidence of any significant injury to the cellular elements of brain parenchyma. This was accomplished by bolus injection of the animal's own blood under pressure via the internal carotid artery. The opening of the barrier was visualized ultrastructurally with horseradish peroxidase showing extracellular spreading of the protein tracer without any evidence of cellular injury. Our studies demonstrated that there is a direct relationship between presence of proteins in the extracellular spaces and increment in water content, indicating that extravasation of serum proteins plays a paramount role in the dynamics of vasogenic brain edema.

The relationship between extravasation of serum proteins and an increase in water content was also demonstrated in epileptiform seizures induced by injection of pentylenetetrazole (PTZ) in rabbits. Areas of the brain showing BBB breakdown to protein tracer revealed consistently a higher content of water in comparison with the adjacent brain tissue samples without BBB damage. At the same time, our studies on PTZ seizures demonstrated an overall reduction of water content of the brain tissue in spontaneously breathing, unrestrained rabbits in which violent muscular convulsions were associated with high elevation of plasma

osmolarity. Such dehydration of the brain tissue, lasting several hours, was not present in artificially ventilated, paralyzed animals which electrophysiologically showed similar intensity of seizures induced by PTZ.

The currently conducted observations on behavior of electrical impedance during and after ischemic injury appear to promise a better understanding concerning the pathophysiology of ischemic lesions. The impedance is measured simultaneously with CBF by an array of electrodes placed in the caudate and cerebral cortex. Additionally monitored are intracranial pressure and electrical neuronal activity. Our studies showed that the onset of ischemia is associated with a prompt rise in electrical impedance. Following release of arterial occlusion, there is a rapid drop in impedance. The drop in impedance is observed also at later stages in ischemic or post-ischemic periods and it is associated with the opening of the BBB and onset of severe ischemic cellular injury. The secondary rise in impedance has been correlated with the elevation of intracranial pressure. Thus, monitoring the electrical impedance from an ischemic lesion may provide crucial information about the pathological phase of the ischemic process. Such information could be useful for designing proper therapeutic measures.

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) and cerebral blood flow (CBF); B) to study the metabolic processes occurring in cerebral ischemia and ischemic edema, especially their prevention and therapy.

A. Ia. During the last year, a major important new model system has been added to the previously described pure cerebrovascular endothelial cultures (see report from 1981-1982) for the studies of cerebral microvascular function and thus for the investigations related to the BBB. It comprised the development and establishment of pure smooth muscle cell culture derived from dissociated cells of microvessels obtained from brains of rats by mechanical dispersion and filtration technique. These cells are metabolically active and possess an adenylate cyclase (AC) responsive to vasoactive substances (so far tested, catecholamines and prostaglandins).

Ib. The characterization of the adrenergic receptors revealed that the cerebrovascular smooth muscle cultures contain specific β_2- and α_1-adrenergic receptors linked to AC. The presence of β_2- but not that of α_1-adrenergic receptors coupled to AC was described in both cerebral microvessels and cultured cerebrovascular endothelium, previously. On the other hand, α_1-adrenergic receptors were implicated in mediating the vasoconstrictive effects of catecholamines which are important in the control of peripheral vascular resistance and blood pressure. Thus, the existence in the cerebrovascular smooth muscles in addition to the β_2- and α_2-adrenergic receptors found in the cerebrovascular endothelium very strongly supports the contention of adrenergic innervation and its involvement in the regulation of CBF and blood pressure.

II. Moreover, the response of endothelial AC to prostaglandins (PGE_1, PGE_2, $PGF_{1\alpha}$, $PGF_{2\alpha}$, PGD_2 and PGI_2) and the relationship of PGE_2 to adrenergic systems were investigated in cerebrovascular endothelial cultures. E-type prostaglandins and PGI_2 were more effective in stimulating endothelial AC (EC_{50} = 3 x 10^{-7}M,

and 3 x 10^{-6}M, respectively) than prostaglandins of the F-series and PGD_2 which activated AC at high doses only. A modulation of endothelial AC response to either PGE_2 or norepinephrine (NE) was observed in the presence of both agents in the system. It was manifested by a dose-dependent NE inhibition of the PGE_2-stimulated formation of cAMP, which was partially restored by phentolamine. Alpha and β-adrenergic agonists (α, clonidine and 6-fluoronorepinephrine; β, isoproterenol) also partly blocked while forskolin and PGE_2 synergistically stimulated the production of cAMP in the endothelial cultures. These findings strongly suggest that the interaction of prostaglandins and α- and β-adrenergic agonists with the AC system in cerebrovascular endothelium may play a role in the regulation of the cerebral microcirculation, blood pressure and/or BBB permeability.

III. The overall existing methodological difficulties in visualization of AC activity in various tissues by light and electron microscopy led to the development of a new histochemical technique for the demonstration of this enzyme. It comprises the stimulation of AC activity by forskolin instead of using nucleotides with or without various hormones (forskolin has been shown by Seamon and Daly, 1981, to increase the level of cAMP formation by direct stimulation of the catalytic unit of the AC). The availability of this method has a great potential for the evaluation of this enzyme in normal and pathological tissues, especially in those cases showing an absence or desensitization of the specific hormonal receptor linkage to AC.

IV. Further studies concerned with the presence of amines in the cerebral microvessels and the cultured cerebrovascular endothelium demonstrated the existence of 5-hydroxytryptamine (5-HT) in both types of tissues by specific immunofluorescence and high pressure liquid chromatography. The cultured cerebrovascular endothelium was found not only to be able to metabolize 5-HT to 5-hydroxyindole acetic acid (5-HIAA), but to synthesize the amine (from its precursor L-tryptophan) which appears to be controlled by prostaglandins. These results provide the first demonstration of extraneuronal 5-HT synthesis in the central nervous system. Although the physiological role of the endothelial synthesized 5-HT is unknown, its vasoactive properties and its interaction with another vasoactive substance (prostaglandins) strongly suggest that it might be involved in the regulation of cerebral microcirculation and/or BBB function.

B. The studies on cerebral ischemia, its pathophysiology, prevention and therapy in gerbils have been concerned with continuous evaluation of the effects of naturally occurring central nervous system depressant [γ-butyrolactone (GBL) and γ-hydroxybutyrate (GHB)] on cerebral ischemia focusing on the elucidation of the possible mechanisms responsible for the observed beneficial effect of GBL and GHB on ischemic brain edema. These investigations showed that the preischemic GHB treatment reduced greatly the ischemically induced changes of the monoamines and their metabolites as well as the accumulation of free tryptophan (the precursor of 5-HT) which correlated well with amelioration of the first phase of cerebral edema. The present experiments which are underway have been centered on evaluating the postischemic administration of GHB and its effect on the monoamines' synthesis and metabolism.

In the Section on Cellular Neuropathology, investigators use immunocytochemical methods to study the distribution of viruses, myelin proteins, and glial constituents in experimental and human demyelinating diseases.

An 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.

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, basic protein (BP) has been localized in dense line regions of both central nervous system and peripheral nervous system 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. Also, myelin associated glycoprotein (MAG) has been localized in compact myelin, a finding of major importance in revising concepts about the role of MAG in the demyelination that is associated with multiple sclerosis.

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. Applications of this technique to open and closed channels ("connexons") at gap junctions show 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 recent work has depended on stop-flow mixing of calcium with phosphatidyl serine liposomes which produces transient cylindrical micelles similar to the cylindrical structures embedded in bilayers at tight junctions.

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. The video light microscopy is being used on isolated squid axoplasm to define the conditions under which small organelles are moving; the axoplasm is frozen under these conditions and examined with freeze-etching or freeze-substitution to determine the relationship of moving organelles to 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. This approach also gives a new, and more exact view of the basic structures of cytoplasm; this background structure is a mixture of fine filaments and granular material which presumably represents the "soluble" cytoplasmic proteins.

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). The specific aim is 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. A new approach under development is to apply metal-based antimony analogues of acetylcholine (which are known to be taken up and released in a manner similar to that of acetylcholine) to active and resting synapses which are then prepared by freeze-substitution and viewed with the electron probe in order to determine where acetylcholine is taken up and stored.

The Section on Neurocytology has been attempting to elucidate further the conditions necessary for optimal survival of allografted neural tissue and its interactions with adjacent brain tissue of the host. Allografts of not only fragments but entire superior cervical ganglia (SCG), transplanted to both young and mature rat recipients, become rapidly vascularized. Eighteen to 24 hours after transplantation, the grafts are infiltrated by blood vessels that can be filled with ink injected from the heart. This filling signifies that the graft's vessels have anastomosed with those of the host's by this time. The "feeder" vessels are derived from the choroid plexus and pia. When the graft is inserted into the cerebellar parenchyma, its intrinsic vessels supply the graft. We have also found histochemically that the enzyme, γ-glutamyl transpeptidase, is present in CNS vessels but not those of normal SCG *in situ*. We are about to see whether CNS vessels, identified in this way, persist in old grafts or whether they are all eventually replaced by regenerated vessels derived solely from SCG vessels. Thus, in addition to a neuronotropic and gliotropic effect, the SCG exerts a powerful angiotropic effect. Preliminary measurements indicate that the permeability of the graft's vessels to a neutral amino acid is intermediate between that of brain and choroid plexus vessels.

In order to characterize the chemical and physical nature of the assembly of intramembranous particles peculiar to astrocytes (and ependymal cells), the first step is to obtain a preparation highly enriched in these cells. The preparation must be monitored to be certain that the isolation procedure itself does not remove the assemblies. Accordingly, cerebral cortex from adult rats were minced and treated, as published methods prescribe, with trypsin. Since this enzyme could alter or remove the assemblies if they are proteinaceous, another batch was not trypsinized. Both lots were then filtered and repeatedly suspended and centrifuged in Ficoll medium. The pellet most enriched with astrocytes was then centrifuged in a Ficoll gradient and a single band removed and monitored by aldehyde fixation, thin sectioning and freeze-fracture. More astrocytes were adherent to each other and there was considerably more debris in the non-trypsinized fraction. The cell membrane and cytoplasm of this and the trypsinized fraction were variably disrupted. Most significantly, the assemblies in the trypsinized membranes were normally distributed, whereas those of the non-trypsinized were tightly clumped. This clumping is the same as that obtained in astrocytes severely damaged *in situ* with a cold probe and by protein denaturants. The cellular aggregates of the non-trypsinized batch were probably damaged mechanically upon filtering. Thus, assembly clumping is a consistent sign of a disrupted cytoskeleton to which the assemblies are attached. With trypsin, the isolation procedure preserves the structure and distribution of the assemblies. The next step is to solubilize these cell membranes for gel electrophoresis.

The mechanism - vesicular transport or opening of tight junctions - whereby the blood-brain barrier to macromolecules is opened, is still uncertain. Since low temperature halts endocytosis in endothelial cells *in vitro*, it was expected that vesicular transport is diminished or stopped, physiologically, in hibernating animals. Accordingly, hibernating ground

squirrels, maintained in a cold room at 8°C, were anesthetized. The brain-core temperature in 13 squirrels ranged from 4°C to 12°C. In the cold room, 2.9 ml of 1.8 M arabinose was infused into one internal carotid artery, followed by 0.6 ml of 35 mg horseradish peroxidase (HRP) and, in 4 animals, by an additional ml of 5 mM lanthanum chloride. The brains were fixed with aldehydes 15 minutes later. All solutions were kept at 5-10°C. In normothermic animals, 1.8 M arabinose invariably opens the barrier: HRP exudes around blood vessels throughout the brain on the infused side. In hypothermic squirrels, most of the parenchymal vessels of the brain did not exude any detectable HRP. Only the large vessels penetrating the brain from the pia were surrounded by HRP which did not spread into the parenchyma. Another consistent finding was a film of HRP on the pial surface. It is, therefore, conceivable that only the pial vessels were affected and that HRP entered the perivascular spaces from the subarachnoid compartment. If reduced temperature "stiffens" the cell membrane so that it cannot invaginate to form endocytotic pits, the membrane may also resist deformation at the tight junctions which remain closed during shrinkage of the endothelium.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02545-02 LNNS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Changes of spontaneous neuronal activity of cortical and hippocampal CA1 neurons

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

T. Yamaguchi, Visiting Fellow, LNNS, NINCDS

COOPERATING UNITS *(if any)*

R. Suzuki, Department of Neurosurgery, Tokyo Medical and Dental University, Tokyo, Japan; 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:
1.1	.6	.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

CHANGES OF SPONTANEOUS NEURONAL ACTIVITY OF CORTICAL AND HIPPOCAMPAL CA1 NEURONS FOLLOWING 5 MINUTE ISCHEMIA IN GERBILS

Activity of cortical neurons and hippocampal CA 1 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. These findings indicate that recovery of neuronal activity after an ischemic insult may still be followed by neuronal death, as late as 3 days after recirculation. Also, these studies show that functional neuronal death may be associated with good structural preservation of the neurons. This project has been completed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02546-02 LNNS

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Behavior of BBB and rCBF in cerebral ischemia produced by MCA occlusion in cats

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
T. Kuroiwa, Visiting Fellow, 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:
1.4	.9	.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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

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. The first opening of the barrier is considered as being due to hemodynamic disturbances produced by reactive hyperemia in areas devoid of autoregulation. The second barrier opening is considered to occur due to some factors derived from severely injured ischemic brain tissue. This project has been completed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02547-02 LNNS

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Observations on behavior of the BBB, rCBF and glucose utilization in gerbils

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
T. Yamaguchi, Visiting Fellow, LNNS, NINCDS

COOPERATING UNITS *(if any)*
R. Suzuki, Department of Neurosurgery, Tokyo Medical and Dental University, Tokyo, Japan; F. Orzi, Neurological Clinic, University of Rome, Italy

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:
1.1	.6	.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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

Morphological changes and changes in cerebrovascular permeability, cerebral blood flow and local cerebral glucose utilization (LCGU) were correlated in gerbils subjected to 5 minute bilateral occlusion of the common carotid arteries. The observations revealed several significant events occurring after the ischemic insult: 1) The acute ischemic destruction of the neurons occurred in a strikingly selective manner in CA1 sector of the hippocampus, 3 days after release of arterial occlusion. 2) There were two openings of the blood-brain barrier, presumably based on two different mechanisms. 3) Ten minutes after recirculation, there was a striking dissociation between cerebral blood flow and utilization of glucose which could be a major cause of injury to neurons occurring during the post-ischemic period. This project has been completed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02548-02 LNNS

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Evaluation of electrical impedance in cerebral ischemia produced by occlusion

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
P. Ting, Special Expert, LNNS, NINCDS

COOPERATING UNITS *(if any)*
Neuronal Interactions Section, 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:
1.6	1.1	.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

EVALUATION OF ELECTRICAL IMPEDANCE IN THE CEREBRAL ISCHEMIA PRODUCED BY OCCLUSION OF THE MIDDLE CEREBRAL ARTERY (MCA) IN CATS

The changes in electrical impedance (EI), which is related to the size of extracellular spaces, were studied in cats subjected to the left MCA occlusion, either permanent or for one hour. The main findings indicate that shortly following MCA occlusion there is a prompt increase of EI due to reduction of extracellular spaces produced by intracellular uptake of interstitial fluid. The release of one hour occlusion is followed by a drop in EI which is due to temporary recovery of the cells and restitution of osmotic balance. The progressive rise in intracranial pressure induces a secondary rise in EI which then after 12-24 hours is followed by a drastic drop in EI signifying enlargement of extracellular compartment produced by ruptures of cell membranes. These studies allow monitoring of basic pathophysiological events occurring during and after an ischemic insult. This may provide an indication for timing various therapeutic approaches which might be different in various stages of an ischemic lesion.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02571-01 LNNS

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Blood-brain barrier breakdown to proteins and water content of brain tissue

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
T. Kuroiwa, Visiting Fellow, 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:
1.1	.6	.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The effect of blood-brain barrier (BBB) breakdown to proteins on the water content of brain tissue was studied in rabbits subjected to unilateral bolus injection of the animal's own blood into the internal carotid artery under pressure. The BBB was assessed with Evans Blue (EB) tracer and with the immunohistochemical peroxidase-antiperoxidase method designed for demonstration of rabbit serum proteins. Also, the penetration of horseradish peroxidase (HRP) tracer, as well as the morphology of the brain tissue, was studied on the electron microscopic level. Water content of the brain tissue was evaluated with a modified specific gravity (SG) method. The results of this study indicate that breakdown of the BBB, allowing entry of serum proteins into extracellular spaces of brain parenchyma, free of any evidence of injury, is associated with a significant increment in water content of this tissue, signifying development of vasogenic brain edema. This type of edema is clinically the most common and important. It is associated with brain tumors, trauma, inflammatory processes and various forms of stroke. Elucidation of the factors responsible for the development of brain edema is imperative in the proper treatment of neurological conditions associated with edema.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02572-01 LNNS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Effect of abolition of BBB opening on water content of ischemic brain tissue

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

P. Ting, Special Expert, 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:
1.1	.6	.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The effect of prevention of reactive hyperemia, which invariably follows release of arterial occlusion in areas of the brain subjected to ischemia of intensity below threshold levels, was evaluated with regard to opening of the blood-brain barrier (BBB) associated with extravasation of serum proteins, and to development of ischemic brain edema. The reactive hyperemia was abolished by hypovolemic withdrawal of the blood at the time of recirculation. Such animals showed no opening of the BBB to proteins and significantly reduced edema, when tested at 3 hours following recirculation, in comparison to edema in normovolemic animals subjected to similar intensity of one hour ischemia. These studies demonstrate further the significance of serum protein extravasation in the development of brain edema.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02573-01 LNNS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Changes in water content of brain and BBB in convulsive seizures

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

R. Cahn, Visiting Fellow, 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:
1.3	.8	.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This study demonstrates that epileptic seizures in unrestrained, spontaneously breathing animals produce very high elevations of osmolarity in blood plasma, for which release of lactic acid produced by muscular contractions appears to be mainly responsible. The high plasma osmolarity induces osmotic dehydration of the brain which lasts for several hours. Elevation of plasma osmolarity and dehydration of the brain are absent in animals in which muscular contractions were pharmacologically abolished and which were artificially ventilated. In both groups of animals, it was evident that the opening of the blood-brain barrier (BBB) to protein tracers induces an increase in water content, which, eventually, may lead to development of edema.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02275-07 LNNS

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Cerebral capillary endothelial cultures. II.

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
M. Spatz, Head, Section on Neurocytobiology, LNNS, NINCDS

COOPERATING UNITS *(if any)*
I. Karnushina, Institute of Biophysics, Biological Research Center, Hungarian Academy of Sciences, Szeged, Hungary

LAB/BRANCH
Laboratory of Neuropathology and Neuroanatomical Sciences

SECTION
Section on Neurocytobiology

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

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

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Cerebral capillary endothelial cultures. II. Adenylate cyclase response to prostaglandins and their interactions with the adrenergic system.

The response of endothelial adenylate cyclase (AC) to prostaglandins (PGE_1, PGE_2, $PGF_{1\alpha}$, $PGF_{2\alpha}$, PGD_2 and PGI_2) and the relationship of PGE_2 to adrenergic systems were investigated in cerebrovascular endothelial cultures. E-type prostaglandins and PGI_2 were more effective in stimulating endothelial AC (EC_{50} = 3 x 10^{-7}M, and 3 x 10^{-6}M, respectively) than prostaglandins of the F-series and PGD_2 which activated AC at high doses only. A modulation of endothelial AC response to either PGE_2 or norepinephrine (NE) was observed in the presence of both agents in the system. It was manifested by a dose-dependent NE inhibition of the PGE_2-stimulated formation of cAMP, which was partially restored by phentolamine. Alpha and β-adrenergic agonists (α, clonidine and 6-fluoronorepinephrine; and β, isoproterenol) also partly blocked while forskolin and PGE_2 synergistically stimulated the production of cAMP in the endothelial cultures. These findings strongly suggest that the interaction of prostaglandins and α- and β-adrenergic agonists with the AC system in cerebrovascular endothelium may play a role in the regulation of the cerebral microcirculation and/or blood pressure.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02324-06 LNNS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Studies on the blood-brain barrier (BBB) to 5-HT and NE metabolites

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

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:
2.6	1.6	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

STUDIES ON THE BLOOD-BRAIN BARRIER (BBB) TO 5-HYDROXYTRYPTAMINE (5-HT) AND NOR-EPINEPHRINE (NE) METABOLITES: CEREBRAL MICROVESSELS AND CAPILLARY ENDOTHELIAL CULTURE, 5-HT METABOLISM AND SYNTHESIS

Further investigations of the 5-HT in cultured cerebrovascular endothelium and isolated cerebral microvessels were concerned with its presence, derivation and/or control. 1) The level of 5-HT in the endothelial cultures could be decreased by incubation with either p-chlorphenylalanine (PCPA), the inhibition of tryptophan hydroxylase or by the addition of indomethacin, the inhibitor of prostaglandin synthesis. Moreover, the indomethacin-induced reduction of endothelial 5-HT was recoverable with the addition of prostacyclin. 2A) The isolated cerebral microvessels obtained either from saline-perfused or unperfused brains of rats pretreated with pargyline [monoamine oxidase (MAO) inhibitor] contained 8.6 and 18.9 pmoles/mg protein, respectively. 2B) The immunofluorescence studies of isolated cerebral microvessels revealed a diffuse and chain-like pattern of immunofluorescence specific for 5-HT.

These findings clearly indicate that the 5-HT present in the microvessels is not only derived from serotonergic nerve endings but it is also formed in the endothelium where its level is most probably controlled by prostaglandin.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02357-05 LNNS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Therapeutic GHB effect on experimental cerebral ischemia in Mongolian gerbils

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

M. Spatz, Head, Section on Neurocytobiology, LNNS, NINCDS

COOPERATING UNITS *(if any)*

C. Maruki, Depatment of Neurosurgery, Juntendo University School of Medicine, Tokyo, 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:
.8	.1	.7

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Recent studies concerned with the effects of preischemic treatment of γ-hydroxybutyrate (GHB), the naturally occurring central nervous system depressant demonstrated that GHB reduces greatly the ischemically induced changes of the monoamines and their metabolites in the brain. Moreover, it reduces the accumulation of free tryptophan (the precursor of 5-HT) which correlated with amelioration of the first phase of cerebral edema induced in the gerbil model. Thus, the present experiments which are underway have been centered on the evaluation of postischemic GHB therapy and its effects on the monoamine synthesis and metabolism in order to elucidate further its beneficial role in ischemia.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02361-06 LNNS

PERIOD COVERED

October1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Investigations on blood-brain barrier (BBB) permeability

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

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	0	0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project has been temporarily discontinued.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02552-02 LNNS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Investigation of extraneuronal catechol synthesizing enzymes in the CNS

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

M. Spatz, Head, Section on Neurocytobiology, LNNS, NINCDS

COOPERATING UNITS *(if any)*

Dr. Ikuko Nagatsu, Fujita-Gakuen Univ. School of Med., Toyoake, Aiche, Japan
Dr. Toshiharu Nagatsu, Tokyo Institutes of Technology, Yokohama, 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:
.8	.1	.7

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Our previous immunohistochemical and biochemical studies of cerebral microvessels and cerebrovascular endothelial cultures showed the presence of phenylethanolamine-N-methyltransferase (PNMT) activity in both tissues. Since these extraneuronal tissues contain a catecholamine synthesizing enzyme which is responsible for conversion of norepinephrine to epinephrine, we extended these studies to determine whether vascular PNMT is indeed capable of producing epinephrine from norepinephrine. For this purpose a direct assay of endothelial epinephrine formed from norepinephrine was determined by using high pressure liquid chromatography. These studies, which are still in progress, have shown that the cultured cerebrovascular endothelium (2nd-4th generation) derived from dissociated cerebral microvascular fractions (obtained from rats) are capable of converting norepinephrine to epinephrine.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02574-01 LNNS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

A new histochemical method for the detection of adenylate cyclase with forskolin

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

G. Szumanska, Guest Worker, 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	.4	.9

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A new histochemical method was developed for the detection of adenylate cyclase (AC) by stimulation of the enzyme activity with forskolin. This method was compared with the technique in which isoproterenol and 5-guanylylimidodiphosphate (GppNp) were used as activators of AC.

The studies revealed that forskolin is not only a suitable activator of AC but is more effective than isoproterenol and GppNp for the demonstration of this enzyme histochemically.

The availability of the method for the detection of AC activity without the necessity of using a hormonal stimulator has a great potential for the evaluation of this enzyme in normal and pathological tissues especially in those cases showing an absence or desensitization of the specific hormonal receptor linkage to AC.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02575-01 LNNS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The establishment of cerebrovascular smooth muscle culture

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

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:
1.2	.1	1.1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This study was concerned with the development and establishment of pure cerebrovascular smooth muscle culture. The established cell line originals from dissociated cells of microvessels obtained from brains of rats by mechanical dispersion and filtration technique.

The cultured cells display histochemical and ultrastructural features characteristic of smooth muscle cells. They are as follows: an ovoid nucleus with one to four nucleoli and a granular slightly basophilic perinuclear cytoplasm which is slightly PAS-positive; prominent myofilaments, many of which are arranged in bundles throughout the cytoplasm, particularly adjacent to the opposing cellular membranes of the cells.

In view of these observations, the cultured cerebrovascular smooth muscle cells provide a new model system for studying their function, especially related to the function of cerebral blood flow, blood pressure and overall to the blood-brain barrier function.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02576-01 LNNS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)* Cerebrovascular smooth muscle cultures: Characterization of adrenergic receptors linked to AC

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

B. Wroblewska, Ph.D., 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:
1.7	.8	.9

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Adrenergic innervation of cerebral microvessels has been implicated in the regulation of cerebral blood flow (CBF) and permeability of blood-brain barrier (BBB). In support of this contention was the demonstration of catecholaminergic receptors linked to adenylate cyclase (AC) in the microvessels and in the cultured cerebrovascular endothelium. Since the control of CBF most likely is not only confined to the endothelium, we investigated the responsiveness of cerebrovascular smooth muscle cell AC to catecholamines. These studies have shown that the catecholamine analogues, zinterol and isoproterenol, were more effective in the stimulation of AC activity than epinephrine and norepinephrine. When the selective antagonists for β_1 and β_2 receptors (β_1-type practolol and atenolol, β_1/β_2-type propanolol and β_2-type butoxamine) were tested against isoproterenol, epinephrine and norepinephrine stimulation of AC activity, the β_1 in contrast to β_2 antagonists were found ineffective. The α-blockers (phentolamine α_1/α_2-type antagonists) and yohimbine (α_2-type antagonist) alone or in the presence of propranolol had not significantly inhibited the catecholamine-induced enhancement of cAMP formation. On the other hand, prazosine (α_1-type antagonist) blocked the stimulatory effect of epinephrine and norepinephrine on AC system. Similarly, the α_2-agonist, clonidine, did not affect the catecholamines' stimulated AC activity while α_1 agonist, phenylephrine, induced a synergistic enhancement of norepinephrine production of cAMP. The findings of β_2- and α_1-type adrenergic receptors in the cultured cerebrovascular smooth muscle provide additional support for the implicated involvement of adrenergic innervation in the regulation of CBF and BBB permeability.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 01995-11 LNNS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Morphological studies of myelin formation, breakdown and regeneration

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Henry deF. Webster, Associate Chief, LNNS, NINCDS

COOPERATING UNITS *(if any)*

Dr. Peter Braun and Dr. Donald Frail
Department of Biochemistry, McGill University, Montreal, Canada

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:
5.3	1.6	3.7

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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. The main effort is directed at mechanisms relevant to human demyelinating diseases. Nervous tissues from experimental animals and humans have been studied in the following sets of current experiments: 1) Use of electron microscopic immunocytochemistry and polyclonal rabbit antisera to localize myelin-associated glycoprotein (MAG). Using post-embedding immunostaining, anti MAG reaction product was found on compact adult CNS myelin. 2) Using the same EM immunocytochemical method with a monoclonal antibody, anti MAG immunoreactivity also was localized in compact CNS myelin. 3) Light and electron microscopic study of serially sectioned mitotic glial cells in developing white matter. The results led us to conclude that developing oligodendroglia probably do not divide while forming myelin sheaths.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02549-02 LNNS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Herpes simplex virus type 2 infection, CNS demyelination, and multiple sclerosis

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

John R. Martin, M.D. Senior Staff Fellow, LNNS, NINCDS

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Neuropathology & Neuroanatomical Sciences

SECTION

Section on Cellular Neuropathology

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.3	1	2.3

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project seeks evidence linking herpesvirus infections, particularly herpes simplex virus type 2 (HSV-2) to the human demyelinating disease, multiple sclerosis (MS). To be plausible, any etiological hypothesis must explain the clinical course, pathology, epidemiology and immunology of MS.

A. Previous work on this project has demonstrated that:

1) HSV-2 strains, including one isolated from the brain of an MS patient, can produce optic nerve, brain and spinal cord demyelination in mice, with many points of pathological similarity to MS.

2) All of the major features of MS epidemiology may be explained by the hypothesis that MS is caused by HSV-2 in a small proportion of people infected with this agent who lack antecedent protective HSV-1 immunity.

B. During FY 1983, studies published or in press establish:

1) Demyelination in experimental HSV-2 infection is part of a spectrum of disease which is consistent with current knowledge of this human agent.

2) HSV-2 persists in neurons and reactivates: may explain MS course.

3) CNS architecture and HSV-2 mechanisms may combine to produce distinctive pathological features similar to those seen in MS.

C. Using virological, immunological, and morphological methods, future studies will use mouse models to aid in understanding the pathogenesis of HSV-2 infection and relation to CNS demyelination, and to devise direct tests of the proposed relation of HSV-2 infection to MS by determining:

1) Whether and under what conditions HSV-2 invades the CNS following genital infection, and if demyelinative pathology follows infection by this route.

2) Patterns of immunity to HSV-2 in mice, and effects of patterns on the outcome of CNS disease.

3) Search for direct evidence of HSV-2 antigen in human CNS tissues in MS.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02550-02 LNNS

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Biochemical and immunologic mechanisms in virally-induced CNS demyelination

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
G. L. Stoner, Senior Staff Fellow, LNNS, NINCDS

COOPERATING UNITS *(if any)*

None

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 *(Use standard unreduced type. Do not exceed the space provided.)*

The goal of this project is the understanding of mechanisms of demyelination occurring in the CNS during viral infections and in experimental allergic encephalomyelitis (EAE). Mechanisms of immunity may be important at two levels: (1) in relation to resistance to viral infection, and (2) in relation to immune-mediated demyelination directed toward viral antigens or self antigens such as myelin basic protein (MBP). The viral infection of the CNS which has been utilized is that of Herpes simplex virus type 1 (HSV-1) or type 2 (HSV-2) in C57/Bl6 mice. The first phase of this work has concentrated on the immunocytochemical detection of HSV antigens. To this end, we have prepared rabbit antisera to HSV-1 and HSV-2 for use in the peroxidase-antiperoxidase (PAP) and biotin-avidin immunocytochemical technique. The antisera can distinguish the two types of HSV in paraffin sections of formalin-fixed infected mouse CNS without prior absorption of the serum by the heterologous viral type. Also, antisera prepared to RK-13 cells infected for 4 or 8 hrs with HSV-1 detect preferentially cytoplasmic antigen, whereas antisera to 18-hr infected RK-13 cells detect primarily nuclear antigen. With these sera expression of viral antigens will be studied in the CNS of normal unimmunized mice and in mice immunized with the homologous or heterologous HSV type. The second aspect of this study concerns the structure and function of MBP in myelin and the effects of viral infection or autoimmunity on its synthesis and incorporation into myelin. A model for MBP structure based on the known amino acid sequence has been proposed. The model suggests that phosphorylation of certain Thr and Ser residues in the nascent polypeptide plays an important role during folding into the native structure of the protein in myelin. Clearly, interference with synthesis or processing of an essential protein such as MBP by virally-induced alteration of cellular functions might seriously compromise the capacity of oligodendrocytes to synthesize and maintain myelin. Elucidation of the molecular mechanimsms which may be operative in a demyelinating disease such as multiple sclerosis is the ultimate goal of this investigation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 01442-17 LNNS

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Permeability of cellular layers in the vertebrate nervous system

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
T. S. Reese, Head, Section on Functional Neuroanatomy, LNNS, NINCDS

COOPERATING UNITS *(if any)*
R. P. Rand, Brock University, St. Catherine's, Ontario, Canada

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:
2.4	.7	1.7

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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 model replaces the previous view that tight junctions are comprised of rows of intramembrane proteins. Instead, the rod-shaped structures are now interpreted as inverted cylindrical micelles of membrane lipids. A similar model now can be applied to tight junctions in invertebrates. Evidence for this model is being gathered from investigations of pure lipid bilayer systems which are induced to form non-planar micellar phases by addition of calcium ion. Cylindrical micelles identical to these postulated at tight junctions are found embedded in these lipid bilayers. Another approach to determining tight junction structure is to explore the true inner surface of naturally occurring tight junctions by deep-etching. A filamentous structure has been found on this surface of the membrane which is coextensive with the cylindrical micelle. This structure is a good candidate for the protein associated with tight junctions, and may explain how cylindrical micelles are stabilized in certain regions of the cell membrane. 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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 01881-13 LNNS

PERIOD COVERED: October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Structural basis of synaptic transmission

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Thomas S. Reese, Head, Section on Functional Neuroanatomy

COOPERATING UNITS *(if any)*
R. M. Gould, N.Y. Psychiatric Institute, Staten Island, N.Y.
D. Landis, Dept. of Neurocytology, Massachusetts General Hospital, Boston, Mass.

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:
2.9	1.4	1.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Most of the accomplishments of this project have now been presented in scientific periodicals. Two new areas of investigation of synaptic structure are underway. New methods have been developed to use rapid freezing to determine how the distribution of calcium in synapses changes in different functional states. Organelles which store and release calcium during secretion as well as sequestering it afterwards have been identified. This work is significant in that it defines the dynamic structure of normal synapses by relating normal variations in structure to different functional states. These approaches to determining the distribution of soluble substances are also being applied to use a new antimony-labeled acetylcholine molecule to determine where acetylcholine is taken up and stored in cholinergic synaptosomes from squid brain. A new method of staining freeze substituted tissue has recently been developed which requires no further stain after the sections are cut, so the stain extends evenly through the section. Therefore the three dimensional structure of the cytoskeleton and related fine filaments in synapses can be determined in continuous serial sections. The locations in the synapses of these filaments by calcium activated proteases is thought to be an important determinant of synaptic shape and function. Differences in the organization of the cytoskeleton and related filaments during synaptic activity are now under investigation in order to determine their role in mobilizing synaptic vesicles for release.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02551-02 LNNS

PERIOD COVERED: October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Structure of neuronal cytoplasm

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation): T. S. Reese, Head, Section on Functional Neuroanatomy, LNNS, NINCDS

COOPERATING UNITS *(if any)*: None

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:
5.9	4.1	1.8

CHECK APPROPRIATE BOX(ES)

- ☐ (a) Human subjects
  - ☐ (a1) Minors
  - ☐ (a2) Interviews
- ☐ (b) Human tissues
- ☒ (c) Neither

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

This project is directed towards determining 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 electron-microscope. Recently these cells have been examined in the living state at very high levels of resolution with a new video microscopic technique developed here; the same preparations are then frozen and examined in the electron-microscope in order to correlate cytoplasmic movements and specific structural features seen in the living state with structures seen in more detail in the same cells in the whole mounts. So far, it has been shown that the cytoplasmic analog consists of fine filaments instead of a microtubular meshwork and that there are distinct cytoplasmic domains characterized by different amounts of Brownean movements and directed movements; positions within the cell; content of organelles; and content, types, and organization of filaments. Methods are being developed to enable immunocytochemical labels to be used to identify key structural components of the cytoplasm. We plan to use this direct method of observing the cytoskeleton to integrate and use these new concepts of cytoplasmic structure to develop a new understanding of the mechanism by which organelles move by fast axoplasmic transport.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 01805-15 LNNS

PERIOD COVERED: October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Membrane Structure of Astrocytes

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
J. Anders 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:
1.6	1.5	0.1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The eventual goal is to characterize the chemical and physical nature of the orthogonal aggregates or assemblies of particles within the cell membranes of astrocytes. The first step is to obtain a cell preparation highly enriched with astrocytes. The preparation must be monitored to be certain that the isolation itself does not alter the morphology of assemblies or remove them. Accordingly, thin slices of cerebral cortex from adult rats were minced and treated with 0.1% acetylated trypsin, as a prescribed step in the isolation; but trypsin could affect the retention of assemblies if they contain protein. The effects of trypsin were, therefore, followed by dividing the minced tissue into a trypsinized and a non-trypsinized fraction. Both fractions were filtered and repeatedly suspended in Ficoll medium and centrifuged. Only the pellet most enriched with astrocytes was differentially centrifuged in a Ficoll gradient, from 7% to 28%, and a single band removed, fixed in 2% glutaraldehyde and divided into two lots: one for thin sectioning and one for freeze-fracture. In the non-trypsinized preparation, more astrocytes adhered to each other and there was more cell debris than in the trypsinized one. In both preparations the cytoplasm and cell membrane were variably damaged. The freeze-fractured replicas revealed that the isolation procedure preserves the assemblies. The plasma membrane of trypsinized cells contained assemblies that were normal in structure and distribution. The assemblies of non-trypsinized cells, however, were markedly clumped. The tight clumping is identical to that in astrocytes denatured or severely injured with a cold probe. Aggregation of assemblies can be caused by agents that disrupt the cytoskeleton. Since the non-trypsinized astrocytes adhere to each other, they must be forced through the filter. The mechanical stresses apparently disrupt the cytoskeleton so that the particles are free to clump. Tightly clumped assemblies, therefore, are a consistent sign of severe cell damage. The normal distribution of assemblies after trypsinization indicates that this step is essential for a greater yield of isolated cell membranes with intact assemblies. The next step is to solubilize these membranes for gel electrophoresis.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02086-10 LNNS

PERIOD COVERED: October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Regeneration in Transplanted Peripheral and Central Neurons

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)

M. W. Brightman, Head, Section on Neurocytology, LNNS, NINCDS

COOPERATING UNITS *(if any)*: Laboratory of Chemical Pharmacology, NCI

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 *(Use standard unreduced type. Do not exceed the space provided.)*

What are the conditions necessary for the successful transplantation of neural tissue to the surface of the brain? We have already defined two requisites: availability of target sites for transplanted neurons and a critical age of the donor. We are examining a third condition: revascularization of the graft. Although dissociated cells can survive in the cerebrospinal fluid, this fluid probably cannot sustain growth of organized tissue. The superior cervical ganglion (SCG) graft, about 1 μm thick, must be revascularized in order to survive. We have been following the re-entry of new vessels into the grafts by filling the vessels with carbon black from the heart and with methacrylate casts of the vascular bed for examination with the scanning electron microscope (SEM). Vessels of the central nervous system (CNS) contain the enzyme γ-glutamyl transpeptidase, detectable histochemically. We have found that the enzyme is not present in the vessels of normal SCG in situ. We can, then, distinguish between the two types of vessels and are processing grafts to see whether the CNS vessels persist or are replaced by the graft's own, intrinsic vessels. In 14 out of 18 grafts, new, patent, vessels invade the SCG allografts only 18 to 24 hours after transplantation. These vessels can be filled from the heart and, therefore, must anastomose rapidly with endothelial sprouts from the pia and choroid plexus. By 48 hours, this revascularization, in terms of total length of vessels, measured with a digitizer, is about 55 $\mu m/\mu m^2$ of tissue. If entire ganglia (about 2mm long) are grafted, a comparably rapid revascularization takes place. As in the SCG fragments, the new vessels usually form a network at the ganglion's periphery where the ganglion cells are situated. When grafts are inserted into the cerebellar substance, revascularization by parenchymal vessels is also brisk. Thus, the SCG graft exerts a rapid and pronounced angiotropic effect on all brain vasculature. Preliminary measurements with the Sokoloff method indicate that the permeability of the graft's vessels to the neutral amino acid, α-aminoisobutyrate, is between that of cerebral vessels and those of the choroid plexus.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02144-09 LNNS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Blood-Brain Barrier

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

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:
1.3	.9	.4

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The mechanism - vesicular transport or opened tight junctions - whereby the blood-brain barrier (BBB) is opened in response to hyperosmotic conditions, is still uncertain. Endocytosis by endothelial cells in vitro is halted at 0.5°C. Thus, in order to diminish, physiologically, vesicular transport by cerebral endothelium in situ, hibernating ground squirrels, kept at 8°C, were used. The brain-core temperature in 13 squirrels ranged from 4°C to 12°C. Cold 2.9 ml of 0.8M arabinose solution was infused into one internal carotid artery. One minute later, 35 mg of horseradish peroxidase (HRP) in 0.6 ml of cold balanced salt solution alone or followed by 1 ml of cold 5 mM lanthanum chloride, was infused. The brains were fixed 15 min later with cold aldehydes. In normothermic animals so treated, the BBB is opened: exudates of HRP and ionic lanthanum appear around arterioles and capillaries throughout the brain on the infused side. The experiment was repeated in a normothermic group (brain temp. about 35°C). The consistent result in all groups was HRP exudation on the pial surface. In hypothermic animals, HRP also exuded primarily around large, penetrating vessels but did not spread into the parenchyma. The pial vessels may have exuded HRP which then entered the perivascular spaces around these larger vessels, from the subarachnoid space. Most parenchymal vessels were unaffected. Arabinose and HRP reached the entire vasculature, because in 2 hibernatng squirrels a mixture of the two was detected throughout the vascular bed after immersion fixation. The results, so far, signify that, since vesicular transport is diminished in hypothermic animals, where the barrier in most vessels is unaffected, barrier opening is due to vesicular transport. However, according to some authors, reduced temperature "stiffens" the cell membrane which cannot invaginate to form vessels. A second interpretation is, then, equally plausible: the tight junctions between cell membranes are less prone to be deformed at 4-12°C during cell shrinkage.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02286-07 LNNS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Mechanism of cerebral hemorrhages

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

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 *(Use standard unreduced type. Do not exceed the space provided.)*

The occurrence of cerebral petechial hemorrhages has been found to differ in feline brains fixed by immersion and perfusion, respectively.

This project has been completed and the manuscript is being readied for publication.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02362-05 LNNS

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)* Effect of DMSO on the histochemical demonstration of glycogen in the perfused-fixed brain

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

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 *(Use standard unreduced type. Do not exceed the space provided.)*

EFFECT OF DIMETHYL SULFOXIDE ON THE HISTOCHEMICAL DEMONSTRATION OF GLYCOGEN IN THE PERFUSED-FIXED BRAIN

This project has been completed and the resulting manuscript has been published.

Cammermeyer, J., and Fenton, I.M.: Factors restricting maximal preservation of neuronal glycogen after perfusion fixation with dimethyl sulfoxide and iodoacetic acid in Bouin's solution. Histochemistry 76: 439-456, 1982.

ANNUAL REPORT

October 1, 1982 through September 30, 1983

Laboratory of Neurophysiology

National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

ANNUAL REPORT

October 1, 1982 through September 30, 1983

Laboratory of Neurophysiology
National Institute of Neurological and
Communicative Disorders and Stroke

Chief

Jeffery L. Barker, M.D.

During the past year work has continued in several different areas of cellular neurobiology, and a multi-disciplinary research program that involves a substantial fraction of the Laboratory's resources has begun.

Dr. Lasansky has continued to examine photic responses and intercellular forms of communication in the vertebrate retina. He has applied circular and annular light stimuli while recording from individual rods and cones and has defined a specific type of synaptic response that involves both cell types. He has spent considerable time and effort developing a relatively new preparation of the vertebrate retina -the retinal slice- that will allow him to study the synaptic communication in detail.

Dr. Wagner has centered most of his efforts on a collaborative project involving the Laboratory of Neuropathology and Neuroanatomical Sciences (project Z01 NS 02548-01). The project is focussed on a multidisciplinary analysis of the pathological consequences of transient and permanent occlusion of the middle cerebral artery in the cat. Correlations in coincident changes in a variety of parameters including brain impedance, central blood flow, intracranial presence, and cell viability have been found.

Dr. Smith has spent much of his time in two areas of research. He has designed, in collaboration with Dr. Ted Colburn, Chief of Instrumentation and Computers Section, ODIR, IRP, NINCDS, an improved version of the single microelectrode voltage-clamp system. At present, the system is being tested for its applicability to cultured mammalian CNS neurons. If applicable, the technique will permit study of neurons not presently accessible to electrophysiological methods allowing the same level of resoltuion. Another area that Dr. Smith has invested time and effort in involves experiments into the membrane site(s) at which conductance mechanisms underlying the generation of action potentials are present. This is an important area for investigation, as it will help to indicate the cellular distribution of two excitable membrane properties crucial to many, if not all, functions of the CNS.

Dr. Barker and colleagues have begun a long-range, multi-disciplinary analysis of the cell biological properties of specific cell types in the CNS. In the process they hope to gain some insight into how certain phenotypic properties come to be expressed during development and then stabilized at maturity. Thus far, the group has purchased a fluorescence-activated cell sorter and developed a number of strategies for sorting subpopulations of cells using flow cytometry. Several experimental avenues appear especially promising, since they allow discrete staining of subpopulations of cells with fluorescent probes.

One involves retrograde labelling of motoneurons and spinothalamic neurons with fluorescent dyes. In this technique dye-coupled protein is taken up by developing neurites and rapidly transported in a retrograde direction to the cell bodies of origin. Sufficient label can be accumulated in cell bodies to provide an adequate signal for sorting. With this method Drs. Anne Schaffner and Paul St. John have begun sorting motoneurons for maintenance in culture, multi-disciplinary analysis, and use in synthesizing immunoreagents specific for motoneurons. Another strategy, used by Drs. Maria Caserta and Paul St. John, involves fixing cell suspensions for fluorescent immunohistochemical reaction with intracellular antigens. Using this method they have conducted a preliminary series of experimental sorts based primarily on transmitters (e.g., opioid peptides), and transmitter-related enzymes (e.g., glutamic acid decarboxylase). Still another technique has been developed by Dr. Gregory Kapatos, who has utilized in vitro immunization techniques to generate a panel of monoclonal antibodies against the surface determinants of prolactin-secreting clonal pituitary cells. The latter were chosen because they express a wide variety of functional transmitter receptors and ion channels. Using biochemical and immunological techniques he has begun to characterize the first two of 20 monoclonal antibodies binding to pituitary cells. With Dr. Maria Caserta he has found that these antibodies bind both to discrete clusters of cells in spinal and supraspinal regions in vivo and to living spinal cord cells in culture and in suspension. He has begun to analyze the immunoreactive spinal cord cells using flow cytometry and has found two distinct subpopulations of cells, defined in terms of light-scattering and fluorescent properties. These will be further examined using biochemical, electrophysiological and morphological techniques.

Drs. Lange, MacDermott, Owen, Redmann and Segal have studied different aspects of excitable membrane properties in cultured CNS neurons and clonal pituitary cells using a variety of electrophysiological recording techniques including two-electrode voltage clamp, patch clamp and whole-cell patch clamp. Dr. MacDermott has set up the newly developed whole-cell patch clamp recording technique for use with cells so small as to be inaccessible to any other method with comparable resolution. She has begun to study the development of excitable membrane properties in cultured CNS neurons. Dr. Lange has spent considerable time and effort in improving all of the computer programs used by the Laboratory for quantitative analysis of electrophysiological data. He has begun to

analyze the changes in membrane conductance induced both by chemical transmitters and drugs and by the membrane potential across the cell. Dr. Owen has studied both chemically and electrically excitable membrane properties. He has found 1) that the mechanism of modulation of GABA-activated Cl^- ion channels by many classes of clinically important drugs involves changes in their kinetics, not their conductances; 2) that in a number of cultured CNS neurons a prominent Ca^{2+}-dependent conductance can be triggered whose role in neuronal function is under study; and 3) that transiently operated K^+ conductances in prolactin-secreting clonal pituitary cells can be regulated by peptides. In addition, he has tested two of the monoclonal antibodies derived from the in vitro immunization protocol set-up by Dr. Kapatos and has found unmistakable effects of both antibodies on excitability. Dr. Redmann, a post-doctoral fellow in the Laboratory of Biophysics, has used the patch-clamp technique to study in detail the kinetics of GABA-activated Cl^- ion channels and the effects of clinically important drugs on these kinetics. Dr. Segal has been especially industrious in investigating excitable membrane properties in cultured CNS neurons. He has found that there are several types of transiently operated K^+ conductance that act in different ways to modulate an important region of membrane potential just subthreshold to the potential at which action potentials are triggered. He has used fluctuation analysis to estimate the properties of Cl^- ion channels activated by GABA in hippocampal cells and has been able to correlate these properties and their sensitivity to drugs with the behavior of putative GABAergic synapses in these cells.

The results obtained during the past year will form the foundation for considering which excitable membrane properties are expressed in what types of sorted cells and how these properties might function to alter synthetic and secretory activities. Eventually we may be able to reconstruct certain synaptic and extra-synaptic forms of intercellular communication. We should also be able to analyze in a systematic and quantitative manner, the development and differentiation of specific CNS neurons. From this research may evolve some new strategies for analyzing in vivo both the physiological basis for certain CNS functions and the cellular mechanisms underlying a variety of CNS dysfunctions.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02019-11-LNP

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Electrophysiological Studies on Neuronal Excitability

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

J.L. Barker, Lab Chief, LNP, IRP, NINCDS

COOPERATING UNITS *(if any)*

Weizmann Institute, Rehovot, Israel; Scripps Institute of Oceanography, California

LAB/BRANCH

Laboratory of Neurophysiology, IRP, NINCDS

SECTION

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
6.0	5.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Experiments using intracellular and extracellular recording techniques have been conducted on cells cultured from the mammalian central nervous system (CNS) and a clonal pituitary line. The work has focussed primarily on characterizing the types of excitable membrane properties resicent in these cells and secondarily on studying the effects of transmitters, hormones and drugs on these properties. The principal conclusions are 1) that multiple types of electrically and chemically excitable membrane properties are present in both cultured central neurons and endocrine cells and 2) that in the case of primary CNS neurons these properties become expressed before birth. Two properties--chemically regulated Cl^- ion conductances and electrically activated transient-type K^+ conductances--have received the most study primarily because these properties are expressed in virtually every nerve cell cultured from spinal and hippocampal regions. The K^+ conductances are also found in clonal pituitary cells. Recent insights into these conductance mechanisms include the following. The kinetics of pharmacologically evoked Cl^- ion channels are markedly voltage-sensitive so that at depolarized potentials more channels open for a longer duration. Synaptically activated Cl^- ion dependent conductances mediated by γ-aminobutyric acid (GABA) show a similar sensitivity to voltage. Thus, GABA-mediated synaptic potentials are effectively more inhibitory at depolarized potentials. In clonal pituitary cells transient-type K^+ conductances, which function to regulate the rate of action potential discharge, are modulated by releasing factor peptides. This modulation accounts for the actions of these peptide hormones in altering the excitability of these cells. Convulsant drugs and transmitters also appear capable of modulating the excitability of central neurons through actions on transient type K^+ conductances. These results provide an initial framework for considering the arrangement of receptors and ion conductance mechanisms in specific types of excitable nerve and endocrine cells.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02330-06 LNP

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Cellular Biological Studies of CNS Neurons

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
J.L. Barker, Chief, LNP, IRP, NINCDS

COOPERATING UNITS *(if any)*
J.H. Neale, Department of Biology, Georgetown University,; R.W. Olsen, Department of Biochemistry, University of California at Riverside

LAB/BRANCH
Laboratory of Neurophysiology, IRP, NINCDS

SECTION

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
7	4.5	2.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Embryonic mouse spinal neurons and clonal rat pituitary cells have been studied with a variety of techniques current in cellular neurobiology, including dissociated cell culture, intact-cell ligand binding, immunohistochemistry, in vitro immunization, hybridoma cloning, immunoblot analysis, retrograde transport of fluorescent label, flow cytometry, and electron microscopy. The initial focus of this project is to develop a successful multi-disciplinary strategy aimed at studying the differentation of specific cellular properties important in neuronal function. Protocols for maintaining dissociated cultures of primary neurons and clonal pituitary cells have been improved. Binding assays to intact central neurons under conditions identical to those used in performing electrophysiological recordings have been performed. New techniques for generating primary immune responses rapidly in vitro have been successfully developed and with these techniques a panel of monoclonal antibodies has been produced. Initial screening shows that two antibodies react specifically with surface antigens present both in cultured clonal pituitary cells and in spinal cord neurons in vivo and in vitro, Accumulation of retrogradely transported fluorescent dye by embryonic motoneurons has been used to provide a signal for fluorescent-activated cell sorting. Flow cytometry has also been used in conjunction with fluorescent immunohistochemical reactions of cells in suspension to provide a quantitative analysis of the development of specific populations of spinal cord cells. Flow cytometric isolation of fluorescently labeled cells should yield relatively pure populations of specific cell types both for use as complex antigen in generating specific immunoreagents and for multidisciplinary analysis. With this multidisciplinary strategy we should be able to study specific types of cells at relatively quantitative levels of analysis and gain some insight into their biological properties, as well as how these properties come to be expressed during embryogenesis and what roles they play in the synthetic and secretory functions associated with the different cell types.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 01659-15 LNP

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Synaptic Contacts of Retinal Neurons

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
A. Lasansky, Chief, Section on Cell Biology, LNP, IRP, NINCDS

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Neurophysiology, IRP, NINCDS

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 *(Use standard unreduced type. Do not exceed the space provided.)*

A depolarizing component of the responses of retinal rods of the turtle to bright annular illumination is a transient and occurs only at the end of the stimulus. The same conditions of stimulation that evoke an off depolarizing transient in the rod responses, result in an after depolarization in the cone responses. The rod depolarization is likely to be due to direct cone input mediated by a rectifying electrical or chemical synapse.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02339-06 LNP

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Neural Coding and Processing of Information in the Visual System

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
H.G. Wagner, Chief, Section on Neuronal Interactions, LNP, IRP, NINCDS

COOPERATING UNITS *(if any)*
Ophthalmology Department, Duke University, Durham, N.C.; 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:
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 *(Use standard unreduced type. Do not exceed the space provided.)*

Work on the characterization of the receptive fields of retinal ganglion cells was suspended during most of this period while the PI was involved in another project.

At the start of this period, work had begun on comparing the sensitivity profiles across the receptive field with fixed intensity response profile.

ANNUAL REPORT

October 1, 1982 through September 30, 1983

Clinical Neurosciences Branch

National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

ANNUAL REPORT

October 1, 1982 through September 30, 1983
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 formulates and conducts basic and applied clinico-investigative research to advance an understanding normal and altered brain-behavior relations, applying electrophysiologic and neuropsychologic procedures to patients with neurologic and neuropsychiatric disorders.

I. Clinical Diagnostic Services:

The principal clinical functions include standard electroencephalographic (EEG) diagnostic services, and computer-derived, evoked potential studies of epilepsy, brain tumors, neuromuscular and neuropsychiatric disorders, and developmental metabolic anomalies. These consultative services are extended to the parent Institute, NINCDS and to other Institutes within NIH. THe sources of referral are listed as follows:

	Diagnostic Services			
Referral Sources	EEG	%	Evoked Potential	%
NINCDS	208	26.1	253	54.3
NIMH	151	19.0	7	1.5
NICHD	60	7.5	9	1.9
NHLBI	22	2.8	1	0.2
NCI	25	3.1	5	1.1
NIAID	38	4.8	20	4.3
NIADDK	5	0.6	3	0.7
NEI	1	0.1	1	0.2
OP (outpatient)	280	35.1	165	35.4
MISC	7	0.9	2	0.4
TOTAL (1263)	797	100.00	466	100.00

The actuarial distribution of EEG and evoked potential evaluations indicate that 60% of the referrals were submitted by NINCDS physicians, the remaining, from other NIH sources. Services identified as miscellaneous represent bedside EEG recording in the CCU, and electrocorticography (ECG) procedures in the neurosurgical suite. Requests for the use of evoked potential studies (visual, brainstem auditory and somatosensory) have increased considerably during this reporting period. This procedure has proven especially useful in the diagnosis and management of demyelinating and related neurologic diseases.

The Branch also provides excellent 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 extends clinical consultation to patients in NINCDS and other Institutes. Standard and specialized 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. A similar paradigm is used to assess drug efficacy, particularly agents which reportedly reduce memory or amnestic impairment in dementia.

II. Research Activities:

Branch members actively conducted several, independent research projects during this reporting period, and in addition, participated in collaboration with other investigators within NINCDS and other Institutes in electrophysiological and neuropsychological procedures.

Clinical seizure patterns elicited with different epileptic disorders continue to be a primary field of research interest. Branch members have been using a standard EEG polygraph in tandem with Video instruments to develop a unique monitoring system which allows the investigators to record crucial ictal, clinical and EEG patterns. This procedure affords an opportunity to simultaneously record observations and events for precise analysis. This system has greatly increased the reliability to correlate EEG and specific seizure patterns, and to document rare electroclinical relations which occur incidentally during routine recordings with epileptic patients.

In collaboration with the Epilepsy Section, positron emission tomography and simultaneous EEG monitoring have been performed with 18flouro2deoxyglucose (FDG) in patients with complex partial seizures; several patients present a normal CT profile and neurological status at examination. The PET scans were unaffected by the seizure frequency, state of alertness, or number of spike discharges. However, a change in antiepileptic medication between interictal scans has been shown to influence the imaged metabolic rate. We are in the process of studying with PET configurations, the action of different antiepileptic drugs. Preliminary analysis suggests that phenobarbital tends to suppress metabolic rate. Our experience also suggests that focal lesions may be detected by the PET scan, even if the EEG abnormality is not well localized. The PET image provides reliable localization of focal abnormalities, this noninvasive procedure is especially valuable in patients with medically intractable seizures, normal neurological and CT examinations, who may be suitable candidates for neurosurgical treatment.

An integrated effort is also being initiated to investigate psychosocial and intellectual problems associated with epilepsy. In an ongoing protocol, patients who have submitted to a unilateral left or right temporal lobe resection for the relief of intractable seizures, 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, mnemonic disorders and the therapeutic effect of surgery. The long term effects of brain surgery on cognitive and emotional processes will be analyzed.

Emotional or affective changes experienced by patients with temporal lobe epilepsy will also be addressed to elucidate the mechanisms of maladaptive behavior. The hypothesis under review posits that left and right brain regulators contribute differentially to emotional perception, judgment and reactions. The integrity of emotive processes is studied by requiring temporal epileptics to perform various affective tasks, while physiological-autonomic events (bilateral skin conductance and heart rate) are recorded. Preliminary results indicate that right temporal patients, while rating affectively colored materials as well as normal, do not exhibit the expected autonomic arousal to pleasant or unplesant materials. The left temporal patients, in contrast, showed reduced emotional, as well as electrophysiological responsivity. Thus it appears that injury to the limbic structures in man tends to produce a state of hypoarousal, and in some instances, a dissociation between what patients 'verbalize' and 'feel' in emotional situations.

To better understand the role of altered perception in this defect, special psychophysical techniques were developed. The preliminary results indicate that perceptual detection, that is, recognition of whether a simple visual stimulus is absent or present, was markedly altered for patients wth right temporal resections. In contrast, left temporal patients did well with this test, but poorly in discriminating 2 versus 1 flash sequences. It appears that the right cerebrum in man deals with stimulus sensitivity and perception, but is less efficient to resolve temporal sequences, a process which depends on the integrity of left brain mechanisms.

To complement these studies which emphasize altered responsivity for early components in evoked potentials, new initiatives have been developed to examine 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. In continued effort at NIH and various laboratories in the country, the origin of this 'central processing' event has been studied, to relate probability judgment with neural correlates. In our laboratory, standard paradigms were applied to patients following temporal lobe removal - as a group, there was no demonstrable defect or change in evoked responses, a finding which challenges current hypothesis that the hippocampus may be a prime generator for the P-300. In the context of other neuropsychological data, the likelihood of frontal regulation has become more attractive, and will be explored. This issue is germane to basic learning and memory, wherein probability judgments shape responses.

Apart from the electrophysiological techniques, a comprehensive neuropsychological study of human aging and the effects of dementia have been completed, describing and comparing cortical and subcortical dysfunctioning in patients with Alzheimer's or Huntington's Disorder. Preliminary impressions indicate that Alzheimer patients are troubled by pervasive, global intellectual decline. These patients did poorly in managing visual, auditory, verbal and nonverbal memory tasks of a short or long term nature, but yielded a pattern of performance which was similar to that for normal individuals, albeit at a greatly reduced level of efficiency.

The initial analysis also showed that the memory impairment for Alzheimer's disease may result from 'poor encoding' of material presented to memory stores. This contrasts sharply wth the basic flaw observed in other amnesic disorders associated with Korsakoff's, head injury or encephalitic conditions where the

deficit involves an inability to store and/or retrieve newly learned experiences or information.

This pattern was not recorded with patients afflicted by Huntington's Disease. With visuospatial judgmental and constructional tasks, these patients did poorly with 'egocentric' tasks, that is, manipulating or perceiving internal space. In contrast, Alzheimer patients were more troubled in handling'allocentric' tasks, that is, perceiving objects or references in external space. These findings are interpreted within the framework of frontal versus parietal lesions respectively, and extend neuropathological impressions of primary degeneration of the fronto-striatal system in Huntington's disease, and posterior, cortical dysfunction, is Alzheimer's disease.

The notion that dementia of the Alzheimer's variety evolves as a unitary disorder is being pressed. The premorbid capabilities and familial stock influence in part, the character and deterioative course of the disorder. Also, it appears that several subgroups may be identified, each with a distinct pattern of neuropsychological deficits and corresponding brain changes.

Laboratory studies have identified 2 orthogonal profiles: patients with a major neurolinguistic or communicative disorder and those with a visuospatial-constructional disorder. In each instance, there was corresponding changes in the form of hypometabolic activity (PETT) in the left temporal-parietal and right posterior parietal zones, respectively. A multi-factorial discriminant analysis of 40 independent cognitive parameters is being undertaken to better identify and diagnose Alzheimer's patients.

Specialized study of neuropsychiatric disorders involved patients with obsessive-compulsive ideation and mannerisms, addressing hypothetical disturbances to frontal brain systems. In collaboration wth NIMH scientists, adolescents and adults with obsessive-compulsive features were studied. 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 frontal lobe integrity and invite conjecture of possible overexcitation of frontal limbic mechanisms in obsessive-compulsive disorders.

In collaboration with clinical investigators in NINCDS and NIMH, developmental irregularities of metabolic disorders and the early effects of radiation of the brain were examined in pediatric patients receiving prophylactic CNS treatments for acute Lymphoblastic Leukemia. Radiographic study of these patents showed dilatation 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 diminshed intellectual competence.

Neuropsychological evaluation of girls with Turner-XD syndrome, before and after hormonal treatment, yielded average intelligence, but in when visuo-spatial, constructive skills. Language and verbal memory were intact and utilized in compensatory fashion. The role of hormones on cognitive development and functions will continue.

Currently, these participants are being studied with evoked-potential procedures

to evaluate physiologic mechanisms, and the effects of hormonal treatments.

In amygdala-kindled rats, we examined a temporal relationship between changes in heart rate and epileptic seizures. The heart rate was monitored by electrodes implanted in the shoulder areas bilaterally. In 14 rats, a total of 47 seizures were studied, and the cardinal finding was slowed heart rate which occurred several seconds after amygdala stimulation and was closely associated with clinical seizures, a few seconds before of after onset. The changes in heart rate lasted between 4 and 28 seconds and ended before clinical seizures ended. Increased heart rate was not observed during the ictal period. Our observation suggests that changes in heart rate may be produced by epileptic seizures, but not by amygdala stimulation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01NS00200-29 CN

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Cognitive and Emotional Profile of Neuropsychiatric Disorders.

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Paul Fedio, Ph.D., Acting Chief, Clinical Neurosciences Branch, NINCDS

COOPERATING UNITS *(if any)*

Experimental Therapeutics Branch, NINCDS

LAB/BRANCH

Clinical Neurosciences, IRP, NINCDS

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 *(Use standard unreduced type. Do not exceed the space provided.)*

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 sectors, utilizing standard and experimental tasks, also establishing normative references for functional changes accompanying the aging processes. These behavioral data will be collated with biochemical and neuroradiometric measures, and independent indicators of deterioration and dementia will be developed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01NS01245-18 CN

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
EEG Learning Correlates Using Scalp and Intracranial Depth Electrodes

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Raymond Johnson, Jr., Ph.D., Psychologist, Clinical Neurosciences, NINCDS

COOPERATING UNITS *(if any)*
Surgical Neurology Branch, NINCDS

LAB/BRANCH
Clinical Neurosciences, IRP, NINCDS

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
2.0	1.0	1.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☒ (a1) Minors
☒ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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 were also evaluated, relating left brain dysfunction to ideational disorders, and right brain activity to maladaptive emotional reactions.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01NS01424-17 CN

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Behavioral Modulation by the Limbic System in Man

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Paul Fedio, Ph.D., Acting Chief, Clinical Neurosciences Branch, NINCDS

COOPERATING UNITS *(if any)*
Surigical Neurology Branch, NINCDS
Neuro-Ophthalmology, Clinical Branch, NEI

LAB/BRANCH
Clinical Neurosciences, IRP, NINCDS

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 *(Use standard unreduced type. Do not exceed the space provided.)*

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 integrity of attentional and perceptual (visual, auditory, and tactile) systems are evaluated using standard and experimental procedures. Physiological events (EEG and skin conductance response) are monitored and recorded during test performance. 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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01NS01658-16 CN

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Hemispheric Development and Specialization of the Intellectual Functions

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)

Paul Fedio, Ph.D., Acting Chief, Clinical Neurosciences Branch, NINCDS

COOPERATING UNITS *(if any)*

Surgical Neurology Branch, NINCDS

LAB/BRANCH

Clinical Neurosciences, IRP, NINCDS

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 *(Use standard unreduced type. Do not exceed the space provided.)*

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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01NS02269-07 CN

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Visual Evoked Potentials in Clinical Neurology and Neuro-Ophthalmology

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Susumu Sato, M.D., Medical Officer, Clinical Epilepsy Section, ETB, NINCDS

COOPERATING UNITS *(if any)*
Clinical Epilepsy Section, ETB, NINCDS

LAB/BRANCH
Clinical Neurosciences, IRP, NINCDS

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 *(Use standard unreduced type. Do not exceed the space provided.)*

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 20-50 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. A half visual field stimulation is used to evaluate the retrochiasmatic visual pathway in normals and patients with various neurological disorders.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01NS02431-04 CN

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Experimental Epilepsy: Seizures Produced by Kindling in Rat

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Shun-ichi Yamaguchi, Ph.D., Psychologist, Clinical Neurosciences, NINCDS

COOPERATING UNITS *(if any)*

Clinical Epilepsy Section, ETB, NINCDS

LAB/BRANCH

Clinical Neurosciences, IRP, NINCDS

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 *(Use standard unreduced type. Do not exceed the space provided.)*

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, and hypoxia on the epileptiform discharges are being investigated, and also the effect of kindled seizures on heart rate and respiration.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01NS02432-04 CN

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Brainstem Auditory Evoked Potentials in Clinical Neurology

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Susumu Sato, M.D., Medical Officer, Clinical Epilepsy Section, ETB, NINCDS

COOPERATING UNITS *(if any)*
Clinical Epilepsy Section, ETB, NINCDS

LAB/BRANCH
Clinical Neurosciences, IRP, NINCDS

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 *(Use standard unreduced type. Do not exceed the space provided.)*

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 20-50 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, 1982 through September 30, 1983
Developmental and Metabolic Neurology Branch
National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

TAB 19

ANNUAL REPORT

October 1, 1982 through September 30, 1983
Developmental and Metabolic Neurology Branch, IRP
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. Development of cellular and animal models of human metabolic disorders. 4. Molecular basis of human lysosomal storage disorders. 5. Transmembrane signalling mechanisms and the role of glycolipids and glycoproteins in this process. 6. The involvement of glycoproteins of the myelin sheath in the development of the nervous system, autoimmune phenomena, and demyelinating diseases. 7. Molecular composition and topographic arrangement of membrane lipids and proteins. 8. Preparation of enzymes that degrade neurotoxic substances.

I. HEREDITARY METABOLIC DISORDERS

A. Molecular Genetics of Gaucher's disease.

We reported last year that we had developed an immunoblotting procedure that permits discrimination between patients with neurologic and non-neurologic forms of Gaucher's disease. This discovery has been extended through the use of monoclonal antibodies to differentiate between the two neurologic phenotypes called Type 2, the infantile form, and Type 3, the juvenile form of this disorder. These developments have extraordinarily important implications for precise genetic counseling and for the design of correct therapeutic strategies to treat patients with the various phenotypes. These investigations are being extended to provide similar discrimination between phenotypes in other sphingolipid storage disorders such as Niemann-Pick disease, generalized (G_{M1}) gangliosidosis, and metachromatic leukodystrophy where nonuniformity of the clinical presentation is frequently encountered.

B. Enzyme Replacement Therapy for Sphingolipid Storage Disorders.

During the past year we were able to obtain highly purified human placental ceramidetrihexosidase in large quantities that are free of contaminating pyrogenic materials. Enzyme replacement trials carried out a number of years ago in patients with Fabry's disease indicated that the intravenous injection of ceramidetrihexosidase caused a reduction in the elevated quantity of ceramidetrihexoside in the patients' blood. This observation was subsequently confirmed independently. However, it was apparent that much larger quantities of enzyme would have to be given to patients with this disorder in order to expect improvement in their clinical status. This investigation was delayed because of pyrogenic substance(s) in the large-scale preparations of ceramidetrihexosidase. These pyrogens have now been eliminated and enzyme replacement therapy for Fabry's disease is under further study at this time.

C. Animal Model of Human Lysosomal Storage Disorder.

We have made significant progress in our understanding of the pathogenesis of the metabolic disorder in the BALB/c mouse mutant that resembles Type C Niemann-Pick disease in humans. The depression of sphingomyelinase and glucocerebrosidase activities in these mice and in this form of Niemann-Pick disease may be a consequence of improper cholesterol metabolism. We have transmitted the disorder to unaffected mice by bone marrow transplantation and we are investigating the effect of marrow replacement in affected animals. We expect that important information will be derived from this investigation not only with regard to pathogenetic mechanisms in lysosomal storage disorders, but with regard to the role of cholesterol in modulating the activity of lysosomal enzymes.

D. Molecular Basis of Human Lysosomal Storage Disorders.

We have determined the amino acid sequence of polypeptides derived from homogeneous preparations of human placental glucocerebrosidase and ceramidetrihexosidase. On the basis of this information, labeled nucleotide probes have been synthesized to monitor the cloning of the genes for these enzymes. Post-translational processing of glucocerebrosidase has been found to be impaired in patients with the neuropathic forms of Gaucher's disease. We have identified the steps required for the lysosomal localization of this enzyme where it is presumed to carry out its physiologic function. Mutations in the structure of the enzyme in patients with the neuropathic forms of Gaucher's disease appear to prevent its correct intracellular targeting.

II. MEMBRANE RECEPTORS FOR ENVIRONMENTAL SIGNALS

Excellent progress has been made in obtaining an understanding of the mechanisms involved in desensitization of cells containing β-adrenergic and trophic hormone receptors and the differentiation of this process from downregulation (loss of receptors). The former reaction is rapid in onset and appears to be caused by a physical change in the receptors that impairs their ability to couple with adenylate cyclase to form cyclic AMP. Downregulation is a slower process that can be induced by hormones and by cyclic AMP and requires protein synthesis.

Further evidence has been obtained for the interaction of gangliosides with the surface glycoprotein fibronectin. Fibronectin binds to a specific region of collagen and mediates the attachment of cells such as fibroblasts to a collagen substratum. Addition of certain gangliosides blocks this interaction in normal cells, whereas exogenous gangliosides are required for fibronectin binding to tumorigenic cells that lack higher ganglioside homologues.

Novel fluorescent probes have been developed to follow the uptake and distribution of exogenous gangliosides. The fluorescent gangliosides become incorporated into the plasma membrane of cells exposed to these reagents. Eventually these gangliosides are endocytosed and accumulate in the perinuclear region of the cells because these derivatives are refractory to enzymatic degradation. These probes should be extraordinarily useful for identifying changes in the composition and distribution of gangliosides in pre-neoplastic and neoplastic cells. A probe based on this technique may eventually be useful to detect cancer cells where changes in ganglioside composition have been recognized for more than a decade.

III. DEMYELINATING DISORDERS

Information on the processing and metabolism of the highly tissue-specific myelin-associated glycoprotein (MAG) progressed rapidly in several unanticipated directions in FY'83. Its selective localization in the periaxonal region of the myelin sheath in the central and peripheral nervous system was confirmed in pharmacologically induced demyelination using iminidodipropionitrile and in the myelin-deficient adult Trembler mouse mutant. The demonstration of the antigenic role of MAG in humans with plasma cell dyscrasias and peripheral neurologic involvement has been confirmed and extended to additional cases. In this situation, the antigenic site of MAG is in the carbohydrate portion of the molecule rather than the polypeptide chain. We have produced a series of monoclonal antibodies to MAG some of which react with the carbohydrate moieties and others with the polypeptide portion of the molecule. An additional discovery concerns the presence of a shared antigenic determinant on human MAG and natural killer (NK) cells. An understanding of the biochemistry of the interaction of MAG with axon membranes and cell-mediated immununological phenomena involving NK cells may be accelerated through identification and determining the amino acid sequence of the common peptide.

IV. MOLECULAR COMPOSITION AND TOPOGRAPHIC ARRANGEMENT OF MEMBRANE LIPIDS.

A novel asymmetric distribution of phospholipids has been observed in human lymphoctyte membranes. This molecular species asymmetry was particularly evident in phosphatidylethanolamine with more highly unsaturated fatty acids being localized on the interior of the plasma cell membrane. Treating lymphocytes with interferon caused a redistribution of the unsaturated species to the exterior of the membrane. These changes appear to correlate with the increase in the natural killing capacity of these cells following treatment with interferon. The studies indicate a significant biochemical response to interferon that may be required for its physiologic and pharmacologic effects.

V. ENZYMES THAT DEGRADE NEUROTOXIC SUBSTANCES

An enzyme system that degrades barbital has been demonstrated in extracts from a soil microorganism. The reactions appear to take place is a concerted complex and it has not been possible to isolate individual protein(s) responsible for this process. We shall continue to try to isolate the catalysts that are involved, and if we are successful, we shall attempt to produce enzymes that degrade other neurotoxins.

CONTRACT NARRATIVE

Developmental and Metabolic Neurology Branch
Intramural Research Program, NINCDS
October 1, 1982 through September 30, 1983

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: $100,840

Objectives: To isolate human placental ceramidetrihexosidase in sufficient purity and quantity for use in enzyme replacement trials in patients with Fabry's disease.

Major Findings: A procedure has been developed for the large-scale purification of human placental ceramidetrihexosidase in sufficient purity and specific catalytic activity so that it can be safely administered to patients with Fabry's disease. During the past year, the contractor succeeded in developing a satisfactory enzyme purification procedure that eliminates contaminating pyrogen(s) that previously prevented administration of large quantities of ceramidetrihexosidase to patients. We have therefore begun enzyme replacement trials with this pyrogen-free enzyme preparation.

Significance to Biomedical Research and to the Program of the Institute: A principal mission of the Institute is to develop effective therapy to treat human diseases. If salutary clinical results can be obtained, an extraordinary milestone will have been accomplished regarding this type of a human genetic disease.

Proposed Course of the Contract: We are reinitiating enzyme replacement therapy in patients with Fabry's disease that has been in abeyance for a decade due to pyrogenic material(s) in the large-scale enzyme preparations that appear to be necessary to obtain a clinically beneficial response. We shall examine the effectiveness of the enzyme in patients with regard to clearance of accumulated ceramidetrihexoside in the liver and in the blood and monitor their clinical responses to this therapeutic agent.

CONTRACT NARRATIVE

Developmental and Metabolic Neurology Branch
Intramural Research Program, NINCDS
October 1, 1982 through September 30, 1983

Contractor: WEIZMANN INSTITUTE OF SCIENCE (NO1-NS-0-2333)

Title: Production of Radiolabeled Glycolipids and Other Sphingolipid Derivatives.

Contractor's Project Director: David Shapiro, Ph.D.

Current Annual Level of Support: $64,050

Objectives: To prepare glucocerebroside, sphingomyelin, and ceramidetrihexoside labeled with ^{14}C in critical portions of the molecule for diagnostic tests for Gaucher's disease, Niemann-Pick disease, and Fabry's disease.

Major Findings: The principal investigator is a world-recognized expert in the chemical synthesis of sphingolipids. He has developed procedures to incorporate radioactive carbon-^{14} into specific portions of sphingolipid molecules. These compounds are used to diagnose patients with the sphingolipid storage disorders listed above, to identify heterozygous carriers of these conditions, to diagnose these disorders prenatally, and to monitor enzyme isolation procedures for glucocerebrosidase, sphingomyelinase, and ceramidetrihexosidase.

Significance to Biomedical Research and to the Program of the Institute: The ability to diagnose patients, identify heterozygotes, and monitor pregnancies at risk for sphingolipid storage disorders represents major contributions to the control of the incidence of these diseases. These procedures are in wide use at the present time.

Proposed Course of the Contract: The contractor will provide radioactive sphingolipids necessary for diagnostic tests and for enzyme purification procedures. He will also develop analogues of sphingolipids for the development of animal models of the human disorders. He will also prepare specific sphingolipid derivatives for use as ligands in affinity column chromatography to expedite and improve the isolation of sphingolipid hydrolases.

CONTRACT NARRATIVE

Developmental and Metabolic Neurology Branch
Intramural Research Program, NINCDS
October 1, 1982 through September 30, 1983

Contractor: GENZYME CORPORATION, BOSTON, MA. (NO1-NS-2-2304)

Title: Preparation of Glucocerebrosidase from Human Placental Tissue

Contractor's Project Director: Henry E. Blair

Current Annual Level of Support: $355,000

Objectives: To isolate human placental glucocerebrosidase in sufficient purity and quantity for use 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 in sufficient purity and specific catlytic activity so that it can be safely administered to patients with Gaucher's disease. The intravenous infusion of this enzyme appears to have retarded the progression of enlargement of the spleen and liver in patients with this disorder, stabilized their blood platelet count, and caused an improvement in the general health and growth patterns of the recipients.

Significance to Biomedical Research and to the Program of the Institute: A principal mission of the Institute is to develop effective therapy to treat human diseases. If the results indicated in the preceding paragraph can be confirmed and extended, an unprecedented feat will have been accomplished regarding human genetic diseases.

Proposed Course of the Contract: We are concluding the control (third) phase of this investigation. Recipients have been randomized; some receive the enzyme and others only the vehicle used to stabilize the preparation. We are also seeking means to improve the targeting of the enzyme to the specific cells in which toxic quantities of lipid accumulate. We shall examine the efficiency of the modified enzyme in patients and we shall continue to attempt to improve the delivery of the enzyme to the central nervous system for the treatment of patients with the neuropathic forms of the disorder.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 00706-24 DMN

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Inborn Errors of Metabolism of Diverse Etiology

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation) John A. Barranger, M.D., Ph.D., Chief, Clinical Investigations and Therapeutics Section, DMNB, NINCDS

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Developmental and Metabolic Neurology Branch

SECTION

Clinical Investigations and Therapeutics

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.3	3.1	0.2

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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 are applied to assist in identifying the less common or new disorders of metabolism. Other phases deal with biochemical observations in known disorders and are designed to elucidate 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. Morphologic correlation is made by light microscopic and ultrastructural studies. Therapeutic trials are conducted in selected disorders. Disorders studied include the lysosomal storage diseases, the leukodystrophies, spinocerebellar degenerations, and amino-acidopathies.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 00815-23 DMN

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Metabolism of Complex Lipids of Nervous Tissue

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Roscoe O. Brady, Chief, 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 *(Use standard unreduced type. Do not exceed the space provided.)*

1. We have made significant progress in characterizing the pathology and abnormal biochemistry of the murine model of Niemann-Pick disease that was identified and developed here. 2. The genetic defect has been shown to be transmitted by bone marrow engraftment into non-involved mice. 3. The metabolic defect in this condition has now been reproduced in cultured skin fibroblasts and the relationship between the accumulation of cholesterol in lysosomes in these cells and the reduction of sphingomyelinase activity under investigation. 4. Elucidation of the mechanism of inhibition of this enzyme by cholesterol should provide a better understanding of the pathogenesis of Niemann-Pick disease which is characterized by deficient sphingomyelinase activity with accumulation of sphingomyelin and cholesterol in the tissues of these patients.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 01309-18 DMN

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Biosynthesis and Function of Glycosphingolipids and Other Glycoconjugates

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Peter H. Fishman, Ph.D., Chief, Membrane Biochemistry Section, DMN, NINCDS

COOPERATING UNITS *(if any)*
Laboratory of Cellular Metabolism, NHLBI
Laboratory of Molecular Biology, NCI

LAB/BRANCH
Developmental & Metabolic Neurology Branch

SECTION
Membrane Biochemistry

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

TOTAL MANYEARS: 2.75	PROFESSIONAL: 1.75	OTHER: 1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Gangliosides appear to be important recognition molecules on the cell surface. In order to explore their dynamics and function, fluorescent derivatives were synthesized. When various viable cells were incubated with the derivatives, their surfaces became highly fluorescent. The fluorescent gangliosides were found to be stably incorporated in the membrane but free to diffuse in the plane of the membrane. The gangliosides could be induced to redistribute by exposing them to appropriate agents such as antibodies or cholera toxin. When cells treated with fluorescent gangliosides were washed and incubated in fresh medium, the surface gangliosides were observed to become internalized and localized in the peri-nuclear region of the cells. An interaction between gangliosides and fibronectin was directly shown by double fluorescence staining. Ganglioside-deficient cells make fibronectin but do not retain it. When the cells were incubated with fluorescent gangliosides and stained with antifibronectin antibodies and a second antibody labeled with a different fluorophore, the gangliosides and the fibronectin exhibited areas of codistribution on the cell surface. Cell surface glycojugates were fluorescently labeled under conditions that maintained cell viability. The cells were treated with sodium periodate which oxidizes cell surface sialic acid residues. The cells were then incubated with Lucifer yellow CH which is a hydrazide. The cells became highly fluorescent and the Lucifer yellow CH was shown to be incorporated into gangliosides and sialoglycoproteins. Prior treatment of the cells with neuraminidase reduced the extent of fluorescent staining. Fluorescently-stained thymocytes were analyzed by fluorescent spectrometry and flow cytometry using a fluorescent activated cell sorter.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 01457-17 DMN

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Chemical Synthesis of Radioactive Sphingolipids

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

A. E. Gal, Chief, Neurochemical Methodology Section, 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:
0.6	0.3	0.3

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Sphingolipids 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 enantimorphic 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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 01480-16 DMN

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Metabolism of Neurohumoral Substances in Marine Animals

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Dr. Norman Salem, Jr., Senior Staff Fellow, DMN, NINCDS

COOPERATING UNITS *(if any)*
None

LAB/BRANCH
Developmental & Metabolic Neurology Branch

SECTION
Physiology and Metabolism Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD. 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 *(Use standard unreduced type. Do not exceed the space provided.)*

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 phenomenon which display an amplification or simplification of human physiological metabolism. The conversion of the polyunsaturated fatty acid docosahexaenoic acid (22:6) into prostaglandin PGF (4-alpha) in the rainbow trout gill was the focus of our current marine studies. Planned explorations of mammalian tissues for this novel prostaglandin and enzymatic system necessitate the purification of the trout gill product in order to characterize chromatographic separation procedures. Success was achieved in producing 22:6 fatty acid metabolites in vitro with the trout gill preparation and in their separation by both TLC and HPLC techniques. Indomethacin, aspirin and boiled controls indicated that the conversions were enzymatic. Preliminary studies indicate that some of these metabolic products are also found in the mammalian CNS and in brain cell cultures.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 01481-16 DMN

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Studies on the Composition and Metabolism of Cellular Membranes

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, or institute affiliation)
Norman Salem, Jr., Ph.D., Senior Staff Fellow, DMN, NINCDS

COOPERATING UNITS *(if any)*
LMI, BRM, NCI-Frederick Cancer Research Facility Toxicology Branch, EPA.

LAB/BRANCH
Developmental and Metabolic Neurology Branch

SECTION
Physiology and Metabolism

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

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.3	2.3	1

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The objective of this project is to elucidate the relationship between molecular composition and topographic arrangements of membrane proteins and lipids with reference to plasma membrane function. Topographic localization of aminophospholipids was assessed by covalent modification with the membrane impermeable reagent trinitrobenzene sulfonic acid (TNBS) using intact cells. In human lymphocytes, a new type of phospholipid asymmetry was observed with respect to fatty acyl composition. This phospholipid molecular species asymmetry evident in phosphatidyl-ethanolamine (PE) with more unsaturated species localized on the plasma membrane interior. When human lymphocytes were treated with interferons, the polyunsaturated PE species migrated to the cell surface. These biphasic changes in membrane composition correlated with biphasic changes in the natural killing capacity of cells treated with interferon. Other membrane functional systems including Mn^{2+}-stimulated ATPase and ATP-dependent Ca^{2+} binding were also investigated in connection with the toxicologic effects of the bioactive agents such as pyrethroids and Mn^{2+}.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 01808-14 DMN

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Glycoproteins of Myelin in Development and Disease

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
R. H. Quarles, Chief, Section on Myelin & Brain Development, DMN, NINCDS

COOPERATING UNITS *(if any)*
Neural and Molecular Ultrastructure Section, LMG, NINCDS
Childrens Hospital Medical Center, Harvard University, Boston, MA.
Dept. Microbiology and Immunology, Queen's University, Kingston, Canada

LAB/BRANCH
Developmental and Metabolic Neurology Branch

SECTION
Myelin & Brain Development

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

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
8.1	4.9	3.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The myelin-associated glycoprotein (MAG) is selectively localized in the periaxonal part of PNS and CNS myelin sheaths where it is likely to be involved in glia-axon interactions. This function was supported by recent immunocytochemical studies in experimental pathological situations (iminodipropionitrile neuropathy and aging quaking mice) showing a correlation between the maintenance of the Schwann cell-axon junction and the presence of MAG. During development, the accumulation of MAG slightly precedes that of P0 glycoprotein in the PNS and myelin basic protein in the CNS, suggesting a function early in the process of myelinogenesis. Metabolic studies in 14-day-old and adult rats have shown that MAG is relatively stable for for 1 to 2 weeks after synthesis and then turns over with a half-life of about 3 weeks. In Trembler mice, affected by severe hypomyelination of the PNS, the amount of MAG in the sciatic nerve is nearly normal but it has a higher apparent molecular weight than control MAG. A panel of monoclonal antibodies reacting with polypeptide and carbohydrate sites on the MAG molecule has now been produced by hybridoma techniques in mice. MAG is the myelin antigen that reacts with monoclonal IgM produced in patients with paraproteinemia associated with peripheral neuropathy. The IgM produced by these patients reacts with human MAG but not rat MAG, and preliminary experiments indicate that the antigenic site is in the carbohydrate portion of the MAG molecule. Several of the experimental mouse IgM monoclonals exhibit the same specificity as that produced by the patients. Recent studies with monoclonal antibodies have also demonstrated a shared antigenic determinant between human MAG and circulating natural killer cells. No evidence of humoral immunity to MAG has been detected in multiple sclerosis patients, but about 20% of these patients show sensitization of peripheral blood lymphocytes to MAG and myelin basic protein in thymidine incorporation studies.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02162-09 DMN

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Synthesis of Compounds Analogous to Glycolipids

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Andrew E. Gal, Ph.D., Chief, Neurochemical Methodology Section, 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:
1.0	0.5	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Conduritol β-expoxide, a saccharide that strongly inhibits β-glucosidases, was synthesized by a method developed by this section that provides the produce 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-expoxide will materially accelerate the identification of the amino acid substitutions (or deletions) that occur in the glucocerebrosidase molecule in patients with Gaucher's disease.

Work was continued on the syntheses of glycolipid analogues of sphingolipids that yield a chromogenic moiety on enzymatic hydrolysis. These compounds are used for the diagnosis and studies of Niemann-Pick, Gaucher's and Krabbe's disease.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02163-09 DMN

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Development of Analytical Methods for the Use of Research of Sphingolipidoses

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
A. E. Gal, Chief, Neurochemical Methodology Section, 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	0.2	0.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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. One of them had as its objective, the determination of gangliosides and other lipids in factor 8 protein fraction, a platelet constituent.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02366-05 DMN

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Regulation of Hormone-Responsive Adenylate Cyclase

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Peter H. Fishman, Ph.D., Chief, Membrane Biochemistry Section, DMN, NINCDS

COOPERATING UNITS *(if any)*

Laboratory of Molecular Biology, NINCDS
Laboratory of Cellular and Developmental Biology, NIADDK

LAB/BRANCH

Developmental & Metabolic Neurology Branch

SECTION

Membrane Biochemistry

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD. 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 *(Use standard unreduced type. Do not exceed the space provided.)*

Exposure of several lines of cultured cells to β-adrenergic agonists leads to a rapid loss in catecholamine-sensitive adenylate cyclase activity (densensitization) followed by a slower loss of β-receptors (downregulation). During desensitization, the receptors appear to uncouple from the cyclase as measured by decreased agonist affinity. β-Recptors from control and desensitization cells were analyzed for activity by membrane/membrane fusion techniques. Adenylate cyclase activity in the donor membranes was inactivated; the membranes were then fused with membranes lacking β-receptors and assayed for β-adrenergic stimulated adenylate cyclase. When the donor membranes were from desensitized cells, there was less activity than when they were from control cells. Thus, desensitization appears to involve a change in the receptor that impairs its ability to couple to adenylate cyclase.

Cycloheximide, chloroquine and monensin inhibited downregulation of β-receptors but not desensitization of adenylate cyclase. Exposure of rat glioma C6 cells to agents that elevate intracellular cyclic AMP (cholera toxin, dibutyryl cyclic AMP) also caused downregulation of the receptors but not desensitization. Similar results were obtained in murine Leydig tumor cells that have receptors for human chorionic gonadotropin (hCG). Cells exposed to hCG became desensitized followed by a biphasic loss of receptors. The first phase depended on occupancy of the receptors by hCG and correlated with internalization and degradation of the bound hormone. The second phase of receptor loss occurred 8 h after exposing the cells to hCG, was independent of receptor occupancy and was mimicked by cyclic AMP. Downregulation of hCG receptors was blocked by cycloheximide, which did not prevent desensitization of hCG-stimulated adenylate cyclase. Thus, desensitization appears to be a hormone-mediated event that does not require protein synthesis whereas downregulation can be induced both by hormones and cyclic AMP and does require protein synthesis.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02433-04 DMN

PERIOD COVERED: October 1, 1982 through September 30, 1983

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.): Models of Lysosomal Storage Disease

PRINCIPAL INVESTIGATOR (List other professional personnel on subsequent pages.)
(Name, title, laboratory, and institute affiliation): John A. Barranger, M.D., Ph.D., Chief, Clinical Investigations and Therapeutics Section, DMNB, NINCDS

COOPERATING UNITS (if any): None

LAB/BRANCH: Developmental and Metabolic Neurology Branch

SECTION: Clinical Investigations and Therapeutics

INSTITUTE AND LOCATION: NINCDS, NIH, Bethesda, MD 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 (Use standard unreduced type. Do not exceed the space provided.)

Human storage disease cells in culture and a mutant G_{M1} 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 added of 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 model as a model for enzyme replacement in neurological disorders is progressing.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02434-04 DMN

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Studies of Lysosomal Function: Receptor-Mediated Pinocytosis of Lysosomal Enzymes.

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

John A. Barranger, M.D., Ph.D., Chief, Clinical Investigations and Therapeutics Section, DMNB, NINCDS

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Developmental and Metabolic Neurology Branch

SECTION

Clinical Investigations and Therapeutics

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD 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 *(Use standard unreduced type. Do not exceed the space provided.)*

The uptake of active glycoprotein lysosomal enzymes occurs, in part, through the mechanism of adsorptive pinocytosis. Receptors for varous 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 utilize 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. Studies 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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02435-04 DMN

PERIOD COVERED: October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Studies On The Mechanism of Pathogenesis Of The Mucopolysaccharidoses.

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
George Constantopoulos, Ph.D., Research Biochemist, DMNB, NINCDS

COOPERATING UNITS *(if any)*
None

LAB/BRANCH
Developmental and Metabolic Neurology Branch

SECTION
Clinical Investigations and Therapeutics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 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 *(Use standard unreduced type. Do not exceed the space provided.)*

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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02453-03 DMN

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Gaucher's Disease: Biochemical and Clinical Studies.

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

John A. Barranger, M.D., Ph.D., Chief,
Clinical Investigations and Therapeutics Section, DMNB, NINCDS

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Developmental and Metabolic Neurology Branch

SECTION

Clinical Investigations and Therapeutics

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
8.6	8	0.6

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Gaucher's disease is the most common lysosomal storage disorder. The carrier frequency has been estimated to be as high as 1 in 12 among Ashkenazi Jews. In addition, because of the unique situation in which the same enzyme deficiency leads to both neurologic and non-neurologic disease, the disorder provides an unusual opportunity for the study of biochemical pathology and the metabolic basis of neurologic disease. More importantly, Gaucher's disease like many other inherited disorders is untreatable.

The aim of these studies is to define the aberrant biochemistry in the group of disorders collected under the eponym of Gaucher's disease and to investigate methods of treating these disorders. As such, this disease serves as the prototype for this group of diseases. Results of these studies will be applicable to the whole group of lysosomal storage disorders.

Studies of the enzymology and protein chemistry of the enzyme deficient in Gaucher's disease, as well, the cellular and molecular biology and genetics will contribute significantly to construction of therapeutic modalities. The clinical disease will be studied by the most current methods. Enzyme and gene replacement will be studied as potential approaches to treatment.

The goal of this proposal is to apply basic scientific data to the treatment of this disorder.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02529-02 DMN

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Development of Enzymes that Inactivate Neurotoxic Agents

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Roscoe O. Brady, M.D., Chief, 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	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02530-02 DMN

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Development of Non-sensitizing Thrombolytic Enzyme Preparations

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Jonathan Newmark, M.D., DMN, NINCDS

COOPERATING UNITS *(if any)*
Department of Biochemistry, Rutgers University
New Brunswick, N. J.

LAB/BRANCH
Developmental and Metabolic Neurology Branch

SECTION
Enzymology and Genetics

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.1	0.1	

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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.

This project has been terminated because of the departure of Dr. Newmark.

TAB 20 -- EXPERIMENTAL THERAPEUTICS BRANCH -- ET/IRP

ANNUAL REPORT

October 1, 1982 through September 30, 1983

Experimental Therapeutics Branch
National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

ANNUAL REPORT
October 1, 1982 through September 30, 1983
Experimental Therapeutics Branch, IRP
National Institute of Neurological and Communicative Disorders and Stroke
Thomas N. Chase, M.D., Chief

The Experimental Therapeutics Branch directs its investigative efforts towards the rational development of improved pharmacotherapies for disorders of the human nervous system. The conceptual approach is to link signs of neurologic dysfunction with abnormalities in a particular neural pathway; novel pharmaceutical strategies are then developed to correct the affected system and thus improve clinical function. Branch research, at both clinical and preclinical levels, remains focused on the dopamine system and closely related transmitter systems in relation to motor and dementing disorders.

During the past year Dr. Thomas N. Chase was appointed Branch Chief and a Unit on Neuroendocrinology was launched under the direction of Dr. Thomas O'Donohue. The Branch is now organized into five closely interactive components: Dr. John Kebabian's Biochemical Neuropharmacology Section conducts basic biochemical and pharmacologic studies of dopamine receptor mechanisms. Dr. Judith Walters' Physiological Neuropharmacology Section evaluates interactions between dopamine-containing neurons and other transmitter pathways within the basal ganglia. Dr. Thomas O'Donohue's Neuroendocrinology Unit investigates peptidergic systems involved in cognitive and motor function. Dr. Thomas Chase's Pharmacology Section explores transmitter abnormalities and pharmacologic interventions in dementing and extrapyramidal disorders. Dr. Roger Porter's Clinical Epilepsy Section conducts clinical pharmacologic studies of convulsive disorders.

BIOCHEMICAL NEUROPHARMACOLOGY SECTION

1. Dopamine Receptor Pharmacology

The Section's standing as a 'world class' center of excellence was reinforced this year. The paper "Dopamine-sensitive adenylate cyclase in the caudate nucleus..." which Dr. Kebabian, the section chief, coauthored with Greengard and Petzold was designated as a citation classic in Current Contents in February 1983. This paper (which was a part of Dr. Kebabian's Ph.D. thesis) was also among the 50-most cited life science papers in the three years following its publication in 1972.

During FY '83, the Section continued to investigate the pharmacology of the D-1 and the D-2 dopamine receptors. The goals of this investigation were three-fold: first, the identification of drugs discriminating between the two categories of dopamine receptor would provide experimental verification of the "two dopamine receptor hypothesis" which originated in ETB in 1979; second, the availability of drugs discriminating between the two categories of dopamine receptor would offer new research tools for investigations of CNS and endocrine physiology conducted either within the Section or within the Branch; and third, structure activity studies of agonist and antagonist pharmacology may provide insight about the structural requirements of the two receptors for either agonists or antagonists.

During FY '83, the Section focused attention upon the pharmacology of the dopaminergic aporphines. S(+)bulbocapnine was shown to be a selective

dopamine antagonist. S(+)bulbocapnine blocks the D-1 receptor but, at the concentrations tested, is devoid of activity upon the D-2 receptor in the intermediate lobe of the pituitary gland. This discovery prompted further investigations of aporphine stereochemistry. The enantiomers of apomorphine as well as N-n-propyl norapomorphine were examined to determine their pharmacological activity upon the D-1 and the D-2 receptor. Both enantiomers of NPA proved to be agonists upon both the D-1 and the D-2 dopamine receptors. Similarly, R(-)APO was an agonist upon both receptors. Interestingly, S(+)APO blocked both the D-1 and the D-2 dopamine receptors. In order to account for the ability of S(+)bulbocapnine and S(+)APO to antagonize the D-1 receptor, an 'N-methyl antagonist hypothesis has been formulated within the Section. According to this hypothesis, compounds containing appropriate stereochemistry at a position corresponding to the 6a carbon of apomorphine and bearing an N-methyl group are capable of blocking the D-1 receptor. This hypothesis accounts for the ability of ergots such as lisuride or lergotrile to block the D-1 receptor. Since S(+)APO also blocks the D-2 receptor, the hypothesis may also be applicable to the D-2 receptor. This hypothesis is being subjected to continuing experimental investigation.

During FY '83, the Section also continued to focus attention upon the selective D-2 agonist LY 141865. The structural features of the molecule responsible for its ability to selectively stimulate the D-2 receptor were identified. The approach used in this endeavour was to examine the pharmacological activity of a series of structural analogues to LY 141865 for activity upon the D-1 and the D-2 receptor. The pyrazole nucleus of LY 141865 could be replaced by a pyrrole without diminishing the specificity towards the D-2 receptor. However, substitution of a catechol for the pyrazole resulted in a compound capable of stimulating either the D-1 or the D-2 receptor. These observations suggest that either a pyrrole or a pyrazole can mimic the effect of a catechol upon the D-2 but not the D-1 receptor.

During FY '83 the Section continued to evaluate the validity of alternative classification schema for dopamine receptors. The hypothesis that the presynaptic autoreceptor for dopamine is an entity distinct from other prejunctional dopamine receptors was evaluated in FY '82. The drug TL-99 is a compound claimed to be selective for the autoreceptor rather than 'postjunctional' dopamine receptors. The compound displays activity in a number of behavioral or biochemical models of the 'autoreceptor' while it is inactive in models of postjunctional dopamine receptors. A prediction of the published data supporting the selectivity of the autoreceptor is that the compound should be inactive upon postjunctional dopamine receptors. In the Section, TL-99 was tested upon two postjunctional dopamine receptors, the D-1 receptor in the carp retina and the D-2 receptor in the intermediate lobe of the pituitary gland. TL-99 proved to be equipotent with dopamine as an agonist upon either postjunctional receptor. These observations failed to provide any support for the hypothesis that the autoreceptor is a distinct pharmacological entity.

2. Intermediate Lobe of the Rat Pituitary Gland

During the past few years, the Section has developed the intermediate lobe (IL) of the rat pituitary gland as a useful system in which to study the D-2 dopamine receptor. In FY '82 the Section continued this ongoing investigation. The IL is an especially useful system because this part of the pituitary gland is innervated by dopaminergic neurons within the hypothalamus. Therefore, studies of the IL dopamine receptor of the effects of dopamine upon the IL utilize a system in which dopaminergic neurotransmission actually occurs.

The IL possesses a beta-adrenoceptor which, when stimulated, initiates a series of events ultimately expressed by the cell as an increase in hormone release. The melanotrophic hormones released from the IL can be quantified by radioimmunoassay and is designated as immunoreactive alpha-MSH (IR-alpha-MSH). Stimulation of the D-2 dopamine receptor inhibits basal hormone release and decreases the responsiveness of the beta-adrenoceptor. In the IL, cAMP metabolism provides a convenient sign of activity at either the beta-adrenoceptor or the D-2 dopamine receptor.

In FY '83, the Section investigated the effects of forskolin upon cAMP formation and hormone release from the IL. Forskolin stimulates adenylate cyclase activity in cell-free homogenates of IL tissue as well as cAMP production by dispersed IL cells. In the same range of concentrations, forskolin also stimulates the release of IR-alpha-MSH from intact melanotrophs. The demonstration that forskolin is rapid acting and that it has the same potency upon hormone release and cAMP production suggests that the forskolin-induced formation of cAMP is directly responsible for forskolin-induced enhancement of hormone release. This contrasts with the response of the IL to beta-adrenergic agonists; these agents are 70-fold more potent as stimulants of hormone release than as stimulants of cAMP production. It is anticipated that forskolin will become an especially useful tool in the search to identify the biochemical mechanism(s) involved in the cAMP -induced enhancement of hormone release.

In FY '83, the Section investigated the alpha-MSH-like peptides in the neurointermediate lobe of the rat pituitary gland. The peptides were separated with HPLC and quantified with RIA. The major immunoreactive material recovered from the IL was identified as N,O diacetyl alpha-MSH by several criteria. First, the material had the same retention time as synthetic N,O-diacetyl alpha-MSH. Second, the material was recognized by antibodies raised against the C-terminal portion of alpha-MSH, but not by antibodies raised against N-acetyl alpha-MSH. Third, after exposure to a strong acid, the material was converted to a peptide possessing the same retention time as alpha-MSH (presumably this is due to the loss of the more labile O-acetyl group). Furthermore, N,O-diacetyl alpha-MSH was identified as the predominant alpha-MSH-like peptide released under basal conditions. When release was stimulated or inhibited with appropriate pharmacological agents, N,O-diacetyl alpha-MSH remained the predominant form of the material released from the cells. These observations did not allow us to endorse the hypothesis of other investigators that the acetylation of alpha-MSH was, in some way, coupled with the release of the hormone from the rat IL.

In FY '83, the Section investigated several consequences of chronic stimulation of blockade of the IL D-2 receptor. Chronic treatment of rats with bromocriptine, a potent D-2 agonists, evokes a series of changes in the IL consistent with a decrease in functional activity. Chronic bromocriptine causes the IL to atrophy. Histological examination reveals that the IL of bromocriptine-treated animals is smaller. Biochemical studies reveal that the content of protein in general and immunoreactive alpha-MSH-like molecules in particular, are decreased by as much as 75%. In addition, the D-2 dopamine receptor is desensitized by treatment with the D-2 agonist; however, the beta-adrenoceptor is unaffected. Biochemical studies also revealed that the capacity of the IL to synthesize melanotrophic hormones was decreased. Chronic treatment with bromocriptine caused a 60% decrease in the amount of messenger RNA directing the synthesis of propiomelanocortin, the prohormone from which the melanotrophic hormones are derived. Likewise, IL cells isolated from bromocriptine-treated rats synthesized 60% less proopiomelanocortin than did the cells isolated from vehicle-treated rats. Similarly, the IL cells from bromocriptine-treated animals synthesize 67% less immunoprecipitable alpha-MSH-like molecules than do the cells isolated from vehicle-treated animals. Conversely, chronic blockade of the IL D-2 receptor was associated with an increase in functional activity. Chronic treatment with spiroperidol increased the capacity of the IL to synthesize proopiomelanocortin and alpha-MSH-like peptides

These observations suggest that the D-2 dopamine receptor can regulate cellular functions in addition to hormone release and cyclic AMP synthesis. Specifically, the D-2 receptor appears to have the capacity to regulate the expression of genetic information by the melanotroph. The mechanism(s) involved in this process have not been characterized.

NEUROENDOCRINOLOGY UNIT

The Unit studies the molecular biology of synaptic chemical transmission in neuropeptidergic neurons. Three projects are now ongoing: (1) identification of peptidergic systems in the brain and spinal cord; (2) pharmacological investigation of peptide action and determination of therapeutic potential for particular peptides; and (3) investigations of the neurobiology of neurons which secrete multiple peptide neurotransmitters.

1. Identification of peptidergic systems in brain and spinal cord

a. Evidence for an endogenous ligand for the phencyclidine receptor

Phencyclidine, PCP, or angel dust is a major drug of abuse. PCP abuse in man often results in clinical manifestations which include euphoria, aggressive behavior and psychotic disturbances which resemble schizophrenia. PCP actions are mediated by interaction with a specific PCP receptor in the brain. Recent experiments in the Unit on Neuroendocrinology have demonstrated the existence of a small peptide from extracts of porcine brain which binds to the phencyclidine receptor. The peptide appears to be a PCP agonist as, like PCP, it causes contralateral turning after unilateral injection into the substantia nigra. Also like PCP, the peptide inhibits activity of cortical and hippocampal neurons when iontophoresed or pressure injected into these regions. The presence of an endogenous ligand to a receptor that, when stimulated, can cause psychotic manifestations is quite interesting. If, in

fact, this peptide is an endogenous ligand for the phencylidine receptor, disorders of this neuronal system could lead to psychopathologies and development of antagonists to this compound could lead to the discovery of a new class of antipsychotic agents.

b. Identification of other peptides in the central nervous system

Two other peptides, bombesin and thymosin, have been identified and characterized in the central nervous system. A monoclonal antibody to bombesin was developed and the distribution of the peptide was determined by immunocytochemistry and by radioimmunoassay in microdissected brain regions. Highest bombesin concentrations were found in the suprachiasmatic nucleus, a region which contains a cluster of bombesin-containing perikarya. Chromatographic studies indicate that bombesin immunoreactivity may actually be due to gastrin-releasing peptide, a larger peptide which contains the bombesin sequence. Thymosin was identified in brain and appears to be in highest concentrations in neurons in the mediobasal hypothalamus.

2. Pharmacology of peptides in the central nervous system

A number of peptidergic systems interact with dopaminergic systems in the brain. Because of the clinical relevance of dopaminergic systems to neurological disorders, the pharmacology of these systems which secrete substance P (SP), neurotensin (NT), secretin (SEC) and bombesin (BN) were investigated.

SP and NT appear to interact with dopaminergic systems in quite different ways. NT has receptors on both perikarya and terminals of the nigrostriatal dopaminergic system as well as terminals of the mesolimbic dopaminergic pathway. In contrast, SP appears to modulate dopaminergic systems primarily in a transsynaptic fashion as SP receptors are on neither dopaminergic terminals or perikarya of the nigrostriatal system. Similar to NT, BN receptors are located in high density in the striatum and particularly high density in the nucleus accumbens.

The unit has recently identified SEC in the brain. An injection of SEC into the lateral ventricle of a conscious rat causes motor changes which include a decrease in open-field locomotor activity which can be reversed by administration of haloperidol, a dopaminergic antagonist. Surprisingly, the SEC action is quite long acting as a single injection causes motor effects for nine days.

3. Studies of multiple neurotransmitter neurons

For the past fifty years, Dale's law has served as an important principle in neurobiology. This principle, which states that one neuron releases only one neurotransmitter, has recently been invalidated. With the discovery of neuropeptides many neurons have been identified which contain and secrete multiple peptides or peptides coexisting with putative non-peptide transmitters. The first multiple neurotransmitter neuron stores and secretes N-acetylated and unacetylated forms of α-melanocyte stimulating hormone (α-MSH), α-endorphin (βE 1-31) and βE 1-27 fragments. Actions of β-endorphin

include induction of analgesia while α-MSH actions include enhancement of arousal, attention, learning and memory. Studies in the unit have been directed at a) presynaptic regulatory processes in these cells b) postsynaptic interactions of α-MSH and β-endorphin and c) pharmacological studies of cognitive effects of α-MSH.

a. Presynaptic regulatory processes

Studies on presynaptic regulation indicate that post-translational modifications of α-MSH and BE can dramatically alter their neuronal actions. N-acetylation of these peptides markedly increases the potency of α-MSH and markedly decreases the potency of BE. Because N-acetylation appears to be a key regulatory step in these cells, the mechanisms for the process was investigated. A single enzyme was identified which acetylates both α-MSH and BE. Furthermore, an effective in vitro acetyltransferase blocker has been synthesized and is currently being tested in vivo. It was also found that presynaptic modification of BE by cleavage of BE 1-31 to BE 1-27 can prevent interactions between BE and α-MSH.

b. Postsynaptic interactions

It was shown that the interactions between α-MSH and β-endorphin are primarily antagonists in nature. Administration of BE or non-opioid C-terminal fragments of BE can block α-MSH induced behavioral effects.

c. Pharmacological studies

Because of the clinical potential for α-MSH in the treatment of cognitive disorders, the behavioral actions of α-MSH and the pharmacology of this action was investigated. It was found that the improvement of cognitive function after α-MSH administration to rats is specific to learning and processing of visual and not auditory information. A number of peptides have been designed, synthesized and tested for behavioral potency. One peptide, Nle-4, D-Phe-7-α-MSH, appeared to be an α-MSH antagonist as it actually debilitated learning in rats. In contrast, a series of cyclic-α-MSH analogues were synthesized which seem to be super-potent α-MSH agonists.

PHYSIOLOGICAL NEUROPHARMACOLOGY SECTION

1. Processes Involved in Modulation of Substantia Nigra (SN) Dopamine Cell Activity

Single unit recording studies have shown that dopamine cells are normally maintained either in a state of tonic activity or in a state of inactivity. An understanding of the processes involved in maintaining dopamine cell activity at its tonic level in the resting animal would provide substantial insight into the issue of which processes might be pharmacologically manipulated in order to alter or modulate this activity. We have been exploring the question of whether the active dopamine cells receive tonic excitatory input. We have found that (-)-baclofen, a drug which blocks transmission at several glutamatergic synapses, slows dopamine cell activity. The neurons in the substantia nigra pars reticulata are 2½ times less sensitive to this drug than are SN pars compacta dopamine neurons. To explore the role of a tonically active glutamatergic innervation of the SN

from the frontal cortex, unilateral transections of frontal cortex were made unilaterally. The concentration of gluatamic acid was decreased after this lesion in the substantia nigra. However, there was no significant change in the activity of the dopamine cells nor in the numbers of spontaneously firing cells per pass after the lesion. On the other hand, considerably fewer active cells were found in the pars reticulate of the substantia nigra. This change in the pars reticulata may result from the loss of glutamatergic input from prefrontal cortex to the SN, or be mediated indirectly via effects of the lesion on other areas, e.g., striatum. The lack of effect of the lesion on dopamine cell activity suggests that dopamine cells are not tonically excited by cortico-nigral innervation. Whether any other excitatory inputs play a role in tonically modulating these cells is a question we continue to explore.

These results and several other lines of evidence suggest that inhibitory processes play the dominant role in modulating dopamine cell activity induced by spontaneously occurring pacemaker potentials. One potential source of such an input is from the large GABAergic efferent cells in the SN pars reticulata which send recurrent axonal collaterals to other cells in the substantia nigra. On the basis of indirect evidence, many researchers have concluded that these pars reticulata neurons exert significant effects on the dopamine cells. Our investigations of the effects of drugs on the activity of these cells suggests, however, that at the least, only a subpopulation of the reticulata neurons may affect the dopamine cells, or that, under some conditions, the influence of this population on the dopamine neurons is strongly overridden by other influences. Studies in which the effects of systemically administered haloperidol, apomorphine and amphetamine on the firing rates of reticulata neurons and population studies of numbers and rates of active cells in the pars reticulata after chronic haloperidol treatment have shown that the activity of at least a major portion of the reticulata cell population changes in the same direction as does the activity of the dopamine cells under these conditions. This suggests that the processes mediating the changes in dopamine cell activity induced by these drugs, whether they involve dopamine autoreceptors, the striatonigral feedback loop, or other processes, play a more important role in regulation of dopamine activity than do the reticulata cells.

We have continued to explore the role of dopamine autoreceptors and the actions of dopamine agonists on the activity of substantia nigra dopamine neurons. Studies have provided additional support for the idea that dopamine autoreceptors mediating inhibitory effects of dopamine agonists on dopamine cell activity are of the D-2 type. LY 141865, a putatively selective D-2 dopamine agonist, consistently inhibits the activity of dopamine neurons. These studies have also indicated that the sensitivity of dopamine cells to inhibition by dopamine agonists is greater than the sensitivity of cells postsynaptic to dopamine neurons to these drugs. Thus, the D-2 receptors mediating the effects of dopamine agonists on postsynaptic neurons may be different, in some respects, from those mediating inhibition of dopamine neurons. Previous studies with $\pm$3-PPP, a dopamine agonist with differing effects on pre- and postsynaptic dopamine receptors support this view, and suggest these receptors may be distinct entities which are potentially separately manipulable pharmacologically.

2. Influence of SN Dopamine Neurons on the Cells of the SN Pars Reticulata and the External Globus Pallidus

Alterations in the inputs to the SN pars reticulata and the globus pallidus, two output nuclei of the basal ganglia, may underlie the symptomology of diseases like parkinsonism, Huntington's chorea and tardive dyskinesia. The SN pars reticulata and globus pallidus share a major striatal input, which is known to be in part GABAergic. In addition to parallel striatal inputs, both nuclei also exhibit potential for direct actions of dopamine: the pars reticulata may be influenced by dopamine released from dendrites of adjacent nigral dopamine neurons, while the globus pallidus is reported to receive a sparse but widespread dopamine innervation from the SN. Previous studies have shown that dopamine can modulate the effects of GABA on pars reticulata and globus pallidus neurons. This finding raised the question of whether dopamine, released from substantia nigra dopamine cell dendrites or nigropallidal dopaminergic projections might act as a neuromodulator which diminishes responses of pars reticulata and globus pallidus neurons to their striatal GABAergic innervation. Recent studies addressing this question have focused on determining whether iontophoresed dopamine, or endogenous dopamine released pharmacologically from SN dopamine dendrites could attenuate the GABA-mediated inhibition of pars reticulata neurons which can be evoked by striatal stimulation. Results showed that iontophoresed dopamine significantly reduces the ability of striatal stimulation to inhibit pars reticulata cell firing. Similarly, amphetamine, which has been shown to release dopamine from dendrites in the SN, was able to significantly attenuate the striatal-evoked inhibition when applied iontophoretically, or systemically. These results provide evidence that the previously described modulatory interaction between dopamine and GABA can occur with physiological release of the two transmitters within the substantia nigra, supporting the idea that dopamine may directly influence SN pars reticulata output neurons.

While globus pallidus neurons respond like the SN pars reticulata cells to iontophoretically applied dopamine, they respond differently to i.v. administration of dopamine agonists in normal animals and in animals in which dopamine neurons have been lesioned, providing an animal model of parkinsonism. Previous studies in this lab revealed that, when given to awake paralyzed rats, a dose of a dopamine agonist, like apomorphine, sufficient to stimulate post-synaptic dopamine receptors significantly increases the firing of neurons in the globus pallidus. However, responses of the cells in the pars reticulata, an area receiving comparable striatal and dopaminergic inputs, were highly variable. Neurons which were identified as nigrothalamic or nigrotectal cells on the basis of antidromic activation from the ventromedial thalamus or superior colliculus also showed highly variable responses.

In contrast, apomorphine caused a more consistent and often total inhibition of firing of both nigrothalamic and nigrotectal neurons in rats in which the dopamine pathway was lesioned unilaterally, while pallidal responses were now variably affected. Thus, in the unlesioned animals, the effect of dopamine receptor stimulation upon the globus pallidus is an apparently uniform one, while the effect upon the SN pars reticulata may involve complex or multiple indirect dopamine-mediated influences. However, in dopamine lesioned rats, the existence of striatal dopamine receptor supersensitivity seems to specifically exaggerate an inhibitory dopamine-

mediated influence upon SN pars reticulata neurons while it appears to exaggerate both inhibitory and excitatory influences upon globus pallidus neurons. These studies indicate that the two regions cannot be considered pharmacologically or functionally analogous nuclei, and suggest that they are differently affected by dopamine receptor stimulation. Appreciation of the mechanisms mediating these differences may lead to more selective therapies for disorders associated with the basal ganglia. In addition, these results indicate that effects exerted through presumed supersensitive receptors, such as those obscured after administration of dopamine agonists to animals with lesioned dopamine systems, are not necessarily simply exaggerations of responses seen in normal animals; they may go in a direction different from that seen in the normal.

PHARMACOLOGY SECTION

The Section conducts clinical and laboratory studies linking the Branch's fundamental research efforts with the neurologic patient. Clinical investigators seek to relate - through cerebral immaging techniques, patient tissue and fluid assays, and selected pharmacologic probes - the status of particular central transmitter systems with signs of extrapyramidal and cognitive dysfunction. Evidence bearing on such relationships provides the basis for preclinical studies of potential pathophysiological mechanisms as well as tests of novel pharmacotherapeutic approaches, especially those involving the dopamine system and closely interacting neural pathways. Diagnostic insights and therapeutic interventions deriving from these laboratory studies then undergo clinical evaluation.

1. Positron Emission Tomography

Positron emission tomography (PET) scanning following fluorodeoxyglucose (FDG) administration provides a non-invasive approach to the study of local neuronal activity within the human central nervous system. These efforts have now been substantially facilitated by the development of a unique, computerized system for the ensemble analysis of patient and control group data. By this means, cerebral metabolic activity can be correlated between multiple, anatomically defined brain regions as well as with a broad array of clinical performance parameters under basal and stimulated conditions. In one application of this technique 20 Alzheimer's patients, who manifested minimal to moderately severe dementia, were compared with 8 age-matched normal subjects. Overall cortical glucose utilization in the Alzheimer's group averaged 10 to 49% below that of the normal individuals. Overall dementia severity and degree of metabolic reduction were closely correlated. No consistent hemispheric asymmetries were discerned in either the Alzheimer's or control groups, although substantial right-left differences were found in some individuals. In contrast with the generally accepted view of this disorder, the posterior parieto-temporal cortex was most severely affected, while the frontal lobes were relatively spared. Whether the observed metabolic changes reflect an abnormality of intrinsic cortical neurons or of nerve cells which project to the cortex remains to be determined.

Tourette syndrome, yet to be associated with any characteristic neuropathologic or biochemical change, has also been studied by the PET-FDG method. Preliminary results suggest no substantial differences in overall cerebral metabolism between patients and control subjects, although in the basal ganglia and portions of the frontal and temporal lobes, mean glucose utilization appeared abnormal.

An attempt to map aspects of human cognitive function has also been undertaken using the PET-FDG method. One study sought to localize aspects of IQ test performance. Wechsler Adult Intelligence Scale (WAIS) subtest scores within the Verbal IQ group or within the Performance IQ group were found to be highly interrelated. With the exception of the Arithmetic and Digit Span subtests, however, there was usually no correlation between the results of any Verbal IQ subtest and any Performance IQ subtest. The cortical distribution of regions in which glucose metabolism was most closely associated with overall Verbal IQ scores centered in the left parasylvian area; similar cortical localization patterns were observed for the Information, Vocabulary, Similarities, and Comprehension subtests. In contrast, overall Performance IQ subtest results localized mainly to the right posterior parietal region as did scores on the Object Assembly, Picture Completion, Block Design, and Digit Symbol subtests. Most WAIS subtests thus appear to evaluate approximately the same abilities (verbal or visual-spatial cognition) and the same cortical areas (left parasylvian or right posterior parietal).

2. Dopamine System

The relation between dopamine system activity and extrapyramidal function remained under active clinical investigation. Based on biochemical and pharmacologic evidence of dopaminergic abnormalities in some forms of dystonia, a study of the dopamine agonist, bromocriptine, was undertaken in 13 patients manifesting this disorder: 7 improved substantially, 1 worsened temporarily, and the remaining 5 had little or no change. Improvement averaged 40% in the responders, and continued unchanged for over 1 year in some individuals. No relation could be found between any clinical factor and the response to bromocriptine.

A decline in motor and cognitive function characteristically attends normal aging. With advancing years, there is also a reduction in brain dopamine, although not to the degree found in parkinsonism. Whether this neurochemical change contributes to the alteration in motor or intellectual performance is not yet known. In an attempt to answer this question, the effect of central dopamine system activation by the oral administration of its metabolic precursor, L-dopa, has been evaluated in 10 healthy individuals who were free of parkinsonism or other neurological deficits. Doses ordinarily used in the treatment of parkinsonism produced no consistent change in motor function, although "effortful" memory improved.

Evidence suggesting that noradrenergic mechanisms influence certain of the antiparkinsonian responses to L-dopa prompted a study of the peripherally acting beta adrenergic blocker, nadolol. The addition of this drug to the patients' regular therapeutic regimen substantially reduced both resting and action tremor. These results not only suggest that beta blockers may be useful in the clinical management of parkinsonian patients with severe tremor but also raise the possibility that adrenergic mechanisms may affect parkinsonian symptoms through their interaction with the dopamine system.

3. GABA System

In a search for specific transmitter abnormalities in senile dementia, cerebrospinal fluid GABA levels were compared in 20 Alzheimer's patients with 15 normal controls. GABA concentrations in the patients averaged 37% below control levels. Moreover, there was a significant positive correlation between degree of GABA decrease and reduction in frontal lobe glucose utilization as determined by the PET-FDG method. On the other hand, the degree of GABA reduction failed to correlate with the severity of most clinical indices of dementia. The results thus suggest that although GABA mediated synaptic function declines in Alzheimer's disease, this change is not a critical determinate for the major functional abnormalities occurring in this disorder.

4. Cholecystokinin System

Cholecystokin octapeptide (CCK-8) coexists with dopamine in some neurons within the basal ganglia, where it may exert a substantial influence on dopaminergic transmission. Recent studies indicate that CCK-8 is rapidly metabolized in rat brain to various intermediate N-terminal and C-terminal fragments. Two of these metabolites, the heptapeptide CCK_{26-32} and the tripeptide CCK_{31-33}, block CCK receptors in the pancreatic ascinar cell and bind to central CCK receptors. Conceivably, CCK mediated synaptic events within the central nervous system may be modulated by one or more physiologically active metabolites of the parent neuropeptide. The possible use of these active fragments as well as their synthetic analogs as pharmacologic tools is now being explored.

Behavioral studies have previously shown that peripherally administered CCK-8 possesses some neuroleptic-like activity. Tolerance to these effects can be prevented by the appropriate spacing of CCK-8 dosing. The presumption that the behavioral changes produced by exogenous CCK-8 are mediated through stimulation of CCK receptors has been strengthened by the finding that dibutyrlcyclic GMP inhibits CCK-8 induced behavioral changes. Ceruletide, a 10 amino acid analog of CCK-8, was found to have somewhat more potent and long lasting behavioral effects than CCK-8. On the other hand, unsulfated CCK-8 evidenced about 100 times less behavioral activity than the naturally occurring, sulfated form of CCK-8. Since both sulfated and nonsulfated CCK-8 appear equipotent at central CCK receptors, but sulfated CCK-8 is much more active peripherally, these results suggest that certain of the behavioral actions of systemically administered CCK-8 may be mediated primarily through peripheral, not central, mechanisms. Clinically, Phase I-II therapeutic trials of ceruletide have now been initiated in patients with neuroleptic-responsive involuntary movement disorders.

5. Substance P System

Preclinical behavioral studies of substance P have continued in collaboration with the Department of Psychology, University of Colorado. Previous investigations have shown that systemically administered substance P enhances the retention of both passive and active avoidance habits and reverses the amnestic effects of electroconvulsive or cycloheximide-induced seizures. Current investigations have focused on the effects of substance P on the acquisition and retention of positively reinforced habits. Available results suggest that substance P given intraperitoneally after training on a T-maze, with food reinforcement, retards reversal learning. In related studies carried out with the Branch's Neuroendocrinology Unit, substance P binding has been characterized and mapped in rat brain.

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 tomography (PET) 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 PET lesions may be identified in some patients even if the EEG abnormality itself is not well localized. In other cases, an ictal PET 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 PET scan is noninvasive and lesions are often documented in patients whose neurological examinations and CT scan are normal. PET may also help to elucidate the effect of seizures on the metabolism of areas outside the seizure focus itself. Clinical correlations can be made with associated data such as the results of neuropsychologic tests and evoked potentials. PET is also being used to study the effect of anti-epileptic drugs on cerebral metabolism.

Intensive monitoring with simultaneous video and EEG recordings continue to elucidate new areas of seizure classification and differentiation. A study of complex partial seizures has been recently concluded. A study of generalized tonic-clonic seizures is underway; 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. Serial spectral analyses of tape recorded EEGs in patients are being studied to help analyze the effects seizure frequency and drugs on cerebral electrical activity. Evoked potentials and EEG have also been used to study children with precocious puberty, some of whom may suffer from cerebral dysrhytmias or clinical seizures.

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.

Clinical Pharmacology of Antiepileptic Drugs.

Pharmacologic studies in epilepsy have concentrated on studies of drug interactions and of new antiepileptic drugs.

The pharmacokinetics of Progabide, a putative GABA agonist, have been studied in 12 normal volunteers. This study showed that Progabide was rapidly absorbed and equally rapidly eliminated, principally by conversion to an acid metabolite. Concentrations of both drug and metabolite were proportional to the dose administered. The half-life of elimination of unchanged drug was approximately 2-4 hours while the acid metabolite was eliminated with a half-life of 6-8 hours. Progabide is currently being evaluated in eight European countries as well as in the United States for its use in epilepsy.

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 both partial seizures and 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. Patients with both seizure types appear to have benefitted. Neuropsychological tests are being performed to help assess the effects of the drug. Initial pharmacologic studies have been performed to derive data on absorption, distribution, and metabolism of flupirtine. It is likely that the current upper limit of dose is inadequate to obtain maximal seizure control.

A number of studies have been performed in drug-interactions of antiepileptic drugs. 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. The combination of carbamazepine and phenytoin is the most effective therapy for complex partial and GTC seizures. Carbamazepine decreased phenytoin clearance by blocking metabolism of the

drug. Significant increases in the plasma levels of phenytoin were seen when these drugs were given in combination. Understanding of this phenomenon could help lead to reduced phenytoin toxicity. Recently completed studies include those on the phenytoin pseudo steady state and the effect of total removal of sedative-hypnotic antiepileptic drugs from patients with severe epilepsy.

When changes in phenytoin dose are made, blood levels may rise or fall to reach a deceptive "pseudo-steady state", followed by further fluctuations before a true steady state is reached. Failure to appreciate this effect may initiate the most assiduous therapeutic efforts.

The study of sedative-hypnotic drug withdrawal showed that these drugs are not necessary, and are potentially toxic, for patients with intractable seizures. Patients do not need to be admitted to the hospitral for drug withdrawal.

CONTRACT NARRATIVE

Experimental Therapeutics Branch, IRP, NINCDS

Fiscal year 1983

Kurt Schlesinger, Ph.D., Department of Psychology, University of Colorado, Boulder, Colorado 80309 (NO1 NS 3-2343)

Title: Murine Behavioral Assays of Novel Peptide Analogs

Date: April 15, 1983 - April 14, 1984

Current Level: $28,000.00

Objectives: To conduct specified behavioral assays in experimental animals of systemically or intracranially administered neuropeptides supplied by the NINCDS.

Methods: A full range of behavioral assays will be carried out involving effects on murine learning and memory, social and sexual behavior, locomotor activity, anticonvulsant and analgesic potency. Motor activity will be evaluated in terms of stereotyped movements and open field behavior. Learning paradigms will include wheel turn, step box, straight alley, consolidation, maze, and reversal training. Analgesic potency will be tested on the hotplate and gridplate. Anticonvulsant activity will be evaluated against chemoconvulsant, electroshock, and audiogenic seizures.

Major Findings: Studies in both inbred and genetically heterogenous mice have revealed that the subcutaneous post-trial administration of substance P reversed the amnestic effects of electroconvulsive shock and cycloheximide. In addition, the peripheral injection of substance P was found to facilitate retention of a single trial passive avoidance habit in animals of both genotypes, provided a weak foot shock was used during training.

Significance to Biomedical Research in the Program of the Institute: The potential for peripherally administered, naturally occurring neuropeptides or their synthetic analogs to modify central synaptic mechanisms may be of importance to the future treatment of neurologic disease. The evaluation of behavioral effects attending pharmacologic manipulation of the substance P system is of particular importance in view of the critical role these neurons play in mediating analgesic, motor, and memory processing in the mammalian central nervous system.

Proposed Course: The efficacy of synthetic substance P analogs will be evaluated during the coming year.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02263 07 ET

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Biochemical and Pharmacological Studies of Dopamine Receptors

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
John W. Kebabian, Chief, Biochemical Neuropharmacology Section, Experimental Therapeutics Branch, IRP, NINCDS

COOPERATING UNITS *(if any)*
Laboratory of Clinical Science, National Institute of Mental Health, ADAMAHA, Bethesda, MD

LAB/BRANCH
Experimental Therapeutics Branch, IRP, NINCDS

SECTION
Biochemical Neuropharmacology Section

INSTITUTE AND LOCATION
NINCDS, Bethesda, MD

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
7.5	7.0	0.5

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The two dopamine receptor hypothesis provides new pharmacological approaches for innovative therapy of disease states. This project investigates the biochemistry of the D-1 and the D-2 dopamine receptors. The knowledge gained about the D-1 and the D-2 receptors may facilitate the development of drugs effective in the treatment of Parkinson's disease, endocrine disorders, psychiatric disorders, hypertension and antiemetics in cancer chemotherapy.

In the search for selective agonists and antagonists of the D-1 and the D-2 receptor, examples of ergolines, partial ergolines, 9-oxdergolines, aporphines, benzazepines and tetralins were examined for their activity on the D-1 and D-2 receptors. Several examples of selective D-1 antagonists were identified.

The biochemical consequences of stimulating the D-2 receptor in the intermediate lobe (IL) of the rat pituitary gland were investigated. The results of this project show that stimulation of this D-2 receptor controls the sensitivity of the D-2 receptor, the size of the IL and the expression of the gene(s) regulating the expression of the proopiomelanocortin gene. Furthermore, these studies provide additional roles for the neurotransmitter, dopamine, within the IL.

The involvement of cAMP in the functioning of the IL was investigated in the current fiscal year. These studies identified forskolin as a useful tool for investigating cAMP metabolism in the IL. The advantage of forskolin over other stimulatory agents is that forskolin is rapid acting and displays the same potency upon cAMP accumulation and hormone release. This property facilitates the design of experiments to determine the role of cAMP in hormone release. Studies of cAMP-dependent protein kinase and the drug-induced changes in its activity were also initiated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02577-01 ET

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Identification and Distribution of Peptides in the Central Nervous System

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Thomas L. O'Donohue, Head, Unit on Neuroendocrinology, Experimental Therapeutics Branch, IRP, NINCDS

COOPERATING UNITS *(if any)*
Biochemistry Department, George Washington University; Pharmacology Department, Howard University; Psychiatry Department, University of Maryland; Clinical Neuroscience Branch, IRP, NIMH

LAB/BRANCH
Experimental Therapeutics Branch

SECTION
Unit on Neuroendocrinology

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
4.25	3.25	1.0

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The largest known class of neurotransmitters is comprised of peptides. The identification of new neuropeptides and the determination of their physiological roles and pathophysiological actions will lead to the development of new pharmacological approaches for the treatment of neurological disease.

A neuropeptide, angel dustin, recently identified in this lab and isolated from porcine brain extracts, is an endogenous agonist for the phencyclidine receptor. Phencyclidine (1-(phenylcyclohexyl piperidine), PCP or angel dust, use in man often results in clinical manifestations which include euphoria, aggressive behavior and psychotic disturbances which resemble schizophrenia.

Angel dustin appears to be a PCP receptor agonist as it has identical electrophysiological actions on rat cortical and hippocampal cells as does PCP; like PCP it also causes contralateral rotation after microinjection in the substantia nigra. It therefore appears likely that in addition to having actions on higher level cortical processes, angel dustin may also have actions on extrapyramidal motor systems. If, in fact, angel dustin is an endogenous ligand for the phencyclidine receptor, disorders of this neuronal system could lead to psychopathologies or motor disorders, and development of antagonists to this compound could lead to the discovery of a new class of antipsychotic agents.

Thymosin and bombesin are two peptides originally identified in non-nervous tissues. Studies is this lab have characterized these peptides in the central nervous system using high pressure liquid chromatography and determined the distribution of these peptides using radioimmunoassay and immunocytochemistry. Thymosin in the brain appears to be highly concentrated in the hypothalamus. Bombesin immunoreactivity in the brain may be due to gastrin-releasing peptide, a larger peptide, which may be the mammalian form of bombesin. Highest concentrations of bombesin are in the hypothalamus where bombesin-containing perikarya emanate from the suprachiasmatic nucleus, a region known to regulate circadian rhythms in mammals.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02578-01 ET

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Pharmacology of Peptides in the Central Nervous System

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Thomas L. O'Donohue, Head, Unit on Neuroendocrinology, Experimental Therapeutics Branch, IRP, NINCDS

COOPERATING UNITS *(if any)*
Biochemical Department, George Washington University; Pharmacology and Medicine Departments, Howard University; Clinical Neuroscience Branch, IRP, NIMH, Digestive Diseases Branch, NIADDK

LAB/BRANCH
Experimental Therapeutics Branch, IRP, NINCDS

SECTION
Unit on Neuroendocrinology

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.7	2.5	1.2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The pharmacological actions of neuropeptides in the central nervous system are studied to determine possible physiological or pathophysiological actions of the peptide and the therapeutic potential of a neuropeptide super-agonist or antagonist. A number of neuropeptide systems are thought to interact with dopaminergic systems in the brain. Because of the clinical relevance of dopaminergic systems to neurological disorders, the pharmacology of these systems which contain and secrete substance P (SP), neurotensin (NT), secretin (SEC) and bombesin (BN) were explored. Receptor assays or radioimmunoassays for each of the peptides were developed by radiolabelling the peptides with iodine or tritium. The distribution of receptors was determined using autoradiographic methods.

SP is found in high concentrations in the striatum and the substantia nigra. Consistently, high densities of SP receptors were found in the striatum but surprisingly, few if any receptors were found in the substantia nigra. It therefore appears that SP modulation of the nigrostriatal dopaminergic system must occur at the level of the striatum. Structure-activity studies of SP indicate that the carboxy-terminus contains the critical sequence of amino acids required for receptor recognition. Unlike SP, it was found that NT has receptors both on perikarya and terminals of the nigrostriatal dopaminergic system. In addition, NT receptors were found on dopaminergic terminals in the nucleus accumbens. Similarly, BN receptors were found in high density in the striatum and particularly high density in the nucleus accumbens.

The laboratory has recently identified SEC in the brain. An injection of SEC into the lateral ventricle of a conscious rat causes motor changes which include a decrease in open-field locomotor activity which can be reversed by administration of haloperidol, a dopaminergic antagonist. SEC receptors were identified in the rat brain and structure activity studies showed that essentially the whole SEC sequence of 27 amino acids is required for receptor binding.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02579-01 ET

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Studies of Multiple Neurotransmitter Neurons

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Thomas L. O'Donohue, Head, Unit on Neuroendocrinology, Experimental Therapeutics Branch, IRP, NINCDS

COOPERATING UNITS *(if any)*
Department of Psychology, John Hopkins University; Department of Chemistry, University of Arizona; Laboratory of Clinical Science, NIMH

LAB/BRANCH
Experimental Therapeutics Branch, IRP, NINCDS

SECTION
Unit on Neuroendocrinology

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.6	2.2	1.4

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

A traditional principle in neurobiology has been that one neuron secretes only one neurotransmitter. With the recent discovery of neuropeptides, many neurons and endocrine cells have been found to synthesize and secrete more than one neurotransmitter or hormone. An important challenge in neurobiology will involve determining the presynaptic and postsynaptic regulatory processes in multiple neurotransmitter neurons.

Opiomelanotropinergic cells and neurons secrete N-acetylated and unacetylated forms of α-melanocyte-stimulating hormone (α-MSH), β-endorphin and β-endorphin fragments. The β-endorphin actions include the induction of analgesia while α-MSH appears to increase arousal, attention, learning and memory. In studies of the behavioral effects of α-MSH in rats we have shown that the cognitive effects are specific to learning of visual and not auditory information. It was also shown that the behavioral effects of α-MSH and β-endorphin are opposite, and that α-MSH behavioral effects can be antagonized by co-administration of β-endorphin.

It was also found that post-translational modification of α-MSH and β-endorphin could markedly alter their neuronal actions. N-acetylation of these peptides markedly increases the behavioral potency of α-MSH and markedly decreases the analgesic potency of β-endorphin. Because N-acetylation appeared to be a key regulatory step, the mechanism for the process was investigated. A single enzyme was identified which acetylates both α-MSH and β-endorphin. It was also found that presynaptic cleavage of β-endorphin 1-31 to β-endorphin 1-27 eliminates the α-MSH antagonistic activity of this peptide.

Because of the clinical potential for α-MSH in the treatment of cognitive disorders, a number of peptides were designed, synthesized and tested for behavioral potency. One peptide, Nle-4, D-Phe-7-α-MSH, appeared to be an α-MSH antagonist as it actually debilitated learning in rats. In contrast, a series of cyclic-α-MSH analogues were synthesized which seem to be super-potent α-MSH agonists.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02139 09 ET

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Pharmacology and Physiology of Central Neurotransmitters

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation) Judith R. Walters, Chief, Physiological Neuropharmacology Section, Experimental Therapeutics Branch, IRP, NINCDS

COOPERATING UNITS *(if any)*

Unit on Neuroendocrinology
Experimental Therapeutics Branch, IRP, NINCDS

LAB/BRANCH

Experimental Therapeutics Branch, IRP, NINCDS

SECTION

Physiological Neuropharmacology

INSTITUTE AND LOCATION

NINCDS, Bethesda, MD

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
5	3	2

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this project is to improve understanding of the role of specific neurotransmitter systems in information processing in the basal ganglia with the goal of developing better strategies for pharmacological treatment of neurological disorders. The following topics are currently under investigation: (1) Processes involved in modulation of substantia nigra (SN) dopamine cell activity. Dopamine neurons have been found to be either tonically active or quiescent under normal conditions. The role of SN pars reticulata GABAergic neurons and corticonigral glutamatergic inputs in regulation of tonic dopamine cell activity is being explored in studies which indicate that neither of these neuronal systems exert a prominent effect on tonic dopamine firing. This supports the potential significance of dopamine autoreceptor-mediated inhibitory processes modulating intrinsically generated spontaneous dopamine cell discharge. (2) Influence of SN dopamine neurons and striatal efferents on the cells of the SN pars reticulata and the external globus pallidus. Alterations in the inputs to the SN pars reticulata and the globus pallidus may underlie symptomatology of Parkinsonism, tardive dyskinesia and Huntington's Chorea. Results have shown that dopamine can modulate the effects of GABA on pars reticulata and globus pallidus neurons. This modulatory interaction between dopamine and GABA can occur with physiological release of the two transmitters within the substantia nigra, supporting the idea that dopamine released from dopamine dendrites may directly influence SN pars reticulata output neurons. While globus pallidus neurons respond like the SN pars reticulata cells to iontophoretically applied dopamine, they respond differently to i.v. administration of dopamine agonists in normal animals and in those in which dopamine neurons have been lesioned, providing an animal model of Parkinsonism. These results suggest these regions cannot be considered pharmacologically or functionally analogous output nuclei of the basal ganglia, and provide insight into the actions of dopamine agonists in Parkinsonism.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02265-07 ET

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Pharmacology, Biochemistry and Physiology of Central Neurotransmitters

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation) Thomas N. Chase, Chief, Pharmacology Section Experimental Therapeutics Branch, IRP, NINCDS

COOPERATING UNITS *(if any)* Dept. of Psychiatry, Univ. of Maryland; Dept. of Pharmacology, Thomas Jefferson Univ; Dept. of Psychology, Univ. of Colorado; Dept. of Psychiatry, Karolinska Institute; Dept. of Neurobiology, Weizmann Institute; Dept. of Psychology, Bloomsburg, Univ. of PA

LAB/BRANCH
Experimental Therapeutics Branch, IRP, NINCDS

SECTION
Pharmacology 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 *(Use standard unreduced type. Do not exceed the space provided.)*

The goal of this project is to develop improved pharmacologic approaches to the treatment of neuropsychiatric disease based on an understanding of the relation between transmitter mechanisms and psychomotor function. These integrated clinical and preclinical efforts are focused on the dopamine system and closely interacting pathways in relation to extrapyramidal and dementing disorders.

1. Positron emission tomography - fluorodeoxyglucose studies of Alzheimer's disease revealed diffuse cortical hypometabolism, most marked in the parieto-temporal association area; the amount of cortical abnormality correlated with the degree of dementia; initial studies of Tourette syndrome suggested a characteristic pattern of cortical and basal ganglia dysfunction; the cortical localization of several cognitive functions, including aspects of language and visual-spatial task performance, has been mapped.

2. Dopamine agonist therapy with bromocriptine was found to improve dystonia in most patients; selective dopamine autoreceptor stimulation by EMD 23448 had no effect on Huntington's chorea; beta-adrenergic blockade with nadolol significantly reduced both resting and action tremor in parkinsonian patients.

3. GABA system abnormalities in Alzheimer's disease were documented in a cerebrospinal fluid study and the GABA agonist, THIP, was evaluated in the rigid variant of Huntington's disease.

4. Cholecystokinin (CCK), a neuropeptide located in some dopamine neurons, was found to be metabolized in rat brain to fragments which bind to central CCK receptors and exert independent activity; in the experimental animal systemic administration of CCK-8 significantly influenced central dopamine metabolism, motor function, and operant behavior. Clinical trials of a CCK-8 analog in patients with dyskinesias has been initiated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02318-06 ET

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Clinical Pharmacology of Antiepileptic Drugs

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

R. J. Porter, Acting Chief, Clinical Epilepsy Section, ETB, IRP, NINCDS

COOPERATING UNITS *(if any)*

Epilepsy Branch, NDP, NINCDS

LAB/BRANCH

Experimental Therapeutics Branch, IRP, NINCDS

SECTION

Clinical Epilepsy Section

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.2	1.2	

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☒ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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. A new protocol for the use of progabide, as well as gamma vinyl GABA, in children with the Lennox-Gastaut syndrome has been approved by the NINCDS-ICRS and will soon be initiated. Both these drugs are thought to act by increasing CNS levels of gamma aminobutyric acid (GABA) a putative inhibitory neurotransmitter. Measurements of changes in CSF GABA levels due to the drugs will be correlated with their effects on seizure control. 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. Carbamazepine was found to decrease phenytoin clearance, leading to significantly higher levels of phenytoin in patients taking both drugs together. Understanding of this effect could help avoid medication toxicity. The pharmacologic evaluation of antiepileptic 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. Future studies are planned to evaluate the specific patterns of hepatic microsomal enzyme metabolism of antiepileptic drugs by evaluating antipyrine metabolites.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02236-08 ET

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Diagnostic and Therapeutic Reevaluation of Patients with Intractable Epilepsy

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
R. J. Porter, Acting Chief, Clinical Epilepsy Section, ETB, IRP, NINCDS

COOPERATING UNITS *(if any)*
Epilepsy Branch, NDP, NINCDS; Office of Administrative Management, Clinical Center, NIH

LAB/BRANCH
Experimental Therapeutics Branch, IRP, NINCDS

SECTION
Clinical Epilepsy Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 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 *(Use standard unreduced type. Do not exceed the space provided.)*

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 tomography (PET) in patients with localized brain lesions has demonstrated focal hypometabolic cerebral areas corresponding to the interictal seizure EEG focus. In some patients, PET has been able to detect a focus when other methods have failed. Studies of patients during partial seizures have shown a change from hypo- to hypermetabolism at the site of the focus. PET may also help to study the effect of seizures on cerebral metabolism beyond the limits of the epileptic focus, as well as the effect of antiepileptic drugs. Future studies using PET will also involve the Lennox-Gastaut syndrome. It is hoped that investigations of cerebral metabolism will lead to better understanding of pathophysiology and improved therapy in this severe encephalopathy of uncertain etiology. PET studies allow more definitive overall identification of the epileptic lesion and suggest new avenues of investigation into the basic mechanisms of the epilepsies. For patients who do not respond to pharmacologic therapy, the section will attempt to study noninvasive means of surgical evaluation. It is hoped that the danger of depth electrode study can be avoided by the use of PET, nuclear magnetic resonance scanning, and magnetoencephalography.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02258-07 ET

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Therapeutic Studies in Parkinsonism and Other Movement Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation) Peter A. LeWitt, Experimental Therapeutics Branch, IRP, NINCDS

COOPERATING UNITS *(if any)*

Laboratory of Clinical Science, NIMH; Adult Psychiatry Branch, Division of Special Mental Health Research, NIMH, Biochemical Pharmacology Section, HE, NHLBI

LAB/BRANCH

Experimental Therapeutics Branch, IRP, NINCDS

SECTION

Therapeutics Section

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD 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 *(Use standard unreduced type. Do not exceed the space provided.)*

This project was terminated at the close of the last Fiscal Year and all active studies were transferred to the Pharmacology Section (Project Number Z01 NS 02265-07 ET), Experimental Therapeutics Branch, NINCDS

ANNUAL REPORT

October 1, 1982 through September 30, 1983

Infectious Diseases Branch
National Institute of Neurological and Communicative Diseases and Stroke

Table of Contents

Table of Contents (cont'd)

ANNUAL REPORT

October 1, 1982 through September 30, 1983
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, mycoplasmaology, 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, 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 high risk children and infections in relation to neonatal deaths and herpesvirus infections in pregnancy. Several studies relate to genital herpes virus infections.

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 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 types of neurological diseases including MS, Epstein-Barr virus infection and myasthenia gravis. Studies are also underway to define the cellular immune responses in MS and other neurological diseases. Special serological investigations of MS and ALS patients are in progress.

Patients with various chronic neurological diseases are being studied for virus antibodies and antigens. These diseases include: postpolio ALS, ALS, polymyositis, and peripheral neuropathy. Patients with ALS are being evaluated with PET scan techniques.

Animal models of chronic CNS infection (coronaviruses) and autoimmunity (EAE) are being used in studies of possible therapeutic materials for MS.

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), Venezuelan equine encephalitis (VEE) and western equine encephalitis (WEE) viruses. A model for congenital toxoplasmosis is in the developmental stages. A model for this disease would allow us to investigate new treatments for this pathogen.

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, and toxoplasmosis are continuing to be investigated.

3. Chronic

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. New studies of simian AIDS (SAIDS) are being conducted to determine the cause of this disease and methods for prevention and treatment. Specimens from AIDS patients are being studied in subhuman primates

C. Section on Neurovirology (NV)

1. Perinatal

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 to 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 non-tumor 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 sought 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.

Studies of AIDS specimens are directed at identifying the causative agent. Investigation of simian AIDS (SAIDS) have demonstrated the transmissability of the disease.

IV. Findings

A. Perinatal

1. Routine TORCH Tests Are Unnecessary In Pregnancy

Analysis of routine TORCH antibody tests shows poor reproducibility for most tests. These tests are unreliable and usually unnecessary. Only rubella testing should be routine.

2. New Latex Test for Rubella Antibody Is Rapid And Specific

A new 8 minute latex test for rubella antibody is very satisfactory for clinical use.

3. Latex Agglutination Test For Group B Streptococcal Antigens Can Detect Antigens In Amniotic Fluid

There findings in expectant monkeys can now be studied in humans for early diagnosis of group B streptococcal infection.

B. Acute

1. Aerosolized Measles Vaccine Effective In Young Children

Aerosolized measles vaccine was found to be superior to subcutaneous vaccine in young children. This is of particular importance in developing subtropical and tropical countries.

2. Rapid Detection of Herpes Simplex Infection By Tissue Culture - Biotin/Avidin Fluorescence

A new method now permits the detection of Herpes simplex virus infection in 24 hours rather than 7 days.

3. Disseminated Strongyloidiasis Infection Can Be Studied In Patas Monkeys

This infection can now be studied in expectant animals. Chemotherapy can now be evaluated.

C. Chronic

1. AIDS - Like Disease Found To Occur Naturally In Rhesus Monkeys

A disease clinically similar to human AIDS was forced to occur in rhesus monkeys housed in one control at the California Primate Research Center, Davis California. This disease provides a valuable model for the studies of human AIDS and investigations of defects in cellular immunity. It is also important in relation to the protection of primates in colonies and zoos.

2. Human Polyomavirus (JC) Produces Glioblastomas In Two Specis of Monkeys

The human polyomavirus, JC, was shown to produce fatal glioblastomas when inoculated into two different species of monkeys - owl monkeys and squirrel monkeys.

3. ELISA Antibody Test Developed For BK Polyoma Virus

A new ELISA test was developed for detecting antibody to BK virus. This method now permits the rapid assay of antibody to this important human virus.

4. Antibody to Human Polyomavirus (BK) Is Not Increased In Mothers Of Children Who Develop Leukemia

ELISA tests of BK polyomavirus antibody in the sera taken during pregnancy from women whose children subsequently developed leukemia did not show increased antibody to the BK virus.

5. Parkinson's Disease Patients Have Normal Antibody Levels To Rubella, Measles, Herpes and Cytomegalovirus

Tests of sera from Parkinson's Disease patients and identical twins showed normal levels of antibody to rubella, measles, herpes and cytomegalovirus.

6. Persistent Varicella - Zoster Infection Produced In Tissue Culture

A new plaque variant was identifed which produces persistent varicella-zoster infection in tissue culture. This provides a new way to study persistence of this virus infection.

7. Coronavirus Antibody Levels Are Normal In MS Patients

Other investigators have reported an association between coronavirus infection and MS. In our studies normal levels of coronavirus antibodies were found.

8. JC Virus Induced CNS Tumors In Owl Monkeys Contain Integrated Viral DNA

The nature of the virus integration suggests that the tumor arises from a single cell. Phenotypic changes in those cells are directly under virus control including: 1) Plasminogen activator secretion, 2) Actin cable disruption and 3) Viral T protein synthesis.

9. Molecularly Cloned JC Virus DNA Gives Rise To Infections Virion Particles When Transfected Into Human Fetal Glial Cells

These findings indicate that the cloning of the JC genome eliminates defective regions in the DNA.

10. BK DNA (Not JC) Is Capable of Replication In Human Embryonic Reading Cells Transformed By An Original Objective Mutant of SV40

This demonstrates that the SV40 T protein distinguishes between BK and JC sequence.

11. Oligoclonal IgG Bands Are Present In The Spinal Fluid of 95% of MS Patients

This test for oligoclonal bands is useful for the diagnoses of MS since 95% of patients have bands, and patients with other neurological diseases rarely have bands.

12. Oligoclonal IgG Bands Develop Early In EAE

Guinea pigs with EAE have oligoclonal bands early in the course of disease. This indicates the involvement of this immune response in EAE.

13. Increase In T Lymphocytes With Thymosin In Patients With Myasthenia Gravis

Patients with myasthenia gravis have an increase in T lymphocytes bearing thymosin during active disease. After thymectomy these cells return to normal levels. These cells maybe a subset of "helper" cells.

CONTRACT NARRATIVE

Infectious Diseases Branch, IRP, NINCDS

Fiscal year 1983

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, the study of herpes, CMV and rubella virus in neurological disease and virus isolation attempts in acquired immunodeficiency syndrome (AIDS) in man and simian acquired immunodeficiency syndrome (SAIDS) in monkeys. The reagents supplied have helped identify the herpes and CMV in a variety of diseases.

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: This contract will be continued for another year.

Publications: None

CONTRACT NARRATIVE

Infectious Diseases Branch, IRP, NINCDS

Fiscal Year 1983

Microbiological Associates: (NO1-NS-3-2316)

TITLE: Development and Delivery of Antigen, Antisera, and Viral Diagnostic Reagents.

Contractor's Project Director: Dr. David A. Fuccillo

Current Funding: $482,500.00

Objectives: This is a service contract to provide research reagents for the papovavirus studies, acquired immune deficiency syndrome (AIDS), simian study of AIDS (SAIDS) and other neurological disease investigations with possible infectious etiology.

Major Findings: Viral diagnostic reagents have been provided for herpes viruses types I and II, cytomegalovirus, measles, rubella, influenza, Coxsackie A and B and varicella. These antigens are used in an attempt to identify the etiology of perinatal and other neurological infections. Enzyme-linked immunosorbent assay (ELISA) tests for detection of IgM to CMV, rubella and toxoplasma have been developed. Reagents for acquired immune deficiency syndrome (AIDS) are being developed to study this highly fatal disease. A similar outbreak of simian AIDS-like disease (SAIDS) has occurred in rhesus monkeys. Reagents to study rhesus monkey CMV and its relationship to SAIDS have been prepared. Reagents for ELISA and hemagglutination tests are being developed for the JC papovavirus. Reagents have been prepared for studies on the molecular genetics of the BK and JC virus.

Significance to the NINCDS Program and Biomedical Research: This contract provides the Infectious Diseases Branch with reagents which are made under standard protocols and with similar cells and strains of viruses from one production lot to another. This allows us to test sera for antibodies from the Collaborative Perinatal Research Project with viruses that were prevalent from 1964 to 1970. Similar production techniques permit data obtained several years ago to be combined with current data. To date, over 80 publications have resulted from analysis of data from these studies. Many of the reports helped establish the frequency of disease during pregnancy, syndromes that develop and information on which to base rational therapeutic and preventive measures. The etiology of AIDS is unknown but data suggests an infectious agent. An animal model would greatly help in understanding its pathogenesis and neurological consequences.

Papovavirus studies provide basic information as to the initiation of viral growth in brain tissue and eventual production of malignancy. These studies may help to explain the host-related mechanism of persistent infection for progressive multifocal leukoencephalopathy (PML) and other slow viral infections.

Proposed Course: The contract will be continued for the next year.

Publications:

Iltis, J.P., Vette, J., Castellano, G.A., Madden, D.L., and Sever, J.L. Persistent varicella-zoster virus infection in a human rhabdomyosarcoma cell line and recovery of a plaque variant. Inf. Immun., 37(1):350-358, 1982.

Shekarchi, I.C., Sever, J.L., Ward, L.A. and Madden, D.L. Microstiks as solid-phase carriers for enzyme-linked immunosorbent assays. J. Clin. Microbiol. 16(6):1012-1018, 1982.

Iltis, J.P., Cleghorn, C.S., Madden, D.L. and Sever, J.L. Detection of antibody to BK virus by enzyme-linked immunosorbent assay compared to hemagglutination inhibition and immunofluorescent antibody staining. Polyomaviruses and Human Neurological Disease, J.L. Sever and D.L. Madden (eds.) Alan R. Liss, New York, N.Y, 1983, p. 157-168.

Iltis, J.P., Castellano, G.A., Gerber, P., Le, C., Vujcic, L.K. and Quinnan, G.V., Jr. Comparison of the Raji cell line fluorescent antibody to membrane antigen test and the enzyme-linked immunosorbent assay for determination of immunity to varicella-zoster virus. J. Clin. Microbiol. 16:878-884, 1982.

Boteler, W.L., Luipersbeck, P.M., Fuccillo, D.A. and O'Beirne, A.J. Enzyme-linked immunosorbent assay for detection of measles antibody. J. Clin. Microbiol. 17(5):814-818, 1983.

CONTRACT NARRATIVE

Infectious Diseases Branch, IRP, NINCDS

Fiscal Year 1983

Microbiological Associates: (NO1-NS-3-2316)

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: Several large lots of media were obtained for use in cellular immunity studies and production of viral antigens. These lots were non-stimulated to human lymphocytes and did not contain substances which stimulated non-specific antigens. Antigens for use in the various types of cell immunity and serological studies were grown in cells produced with a lot of fetal calf serum previously obtained on this contract 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 lots of serum and the use of these reagents in the test itself reduces the nonspecific reactions. This allows us to determine more accurately the specific reactions. 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: The contract will be continued for another year.

Publications: None

CONTRACT NARRATIVE

Infectious Diseases Branch, IRP, NINCDS

Fiscal Year 1983

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 - examples: owls Aotus trivirgatus, squirrels Saimiri sciureuis, rhesus Macaca mulatta, patas Erythrocebus patas, cynomologus 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 of nonhuman 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, collects specimens as required by protocols, and performs the necropsies 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: This contract will be continued for the following year to provide the isolated housing and care of a colony of nonhuman 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.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01-NS-00402-27-ID

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Perinatal Infections Causing Damage to the CCP Project

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
John L. Sever Chief 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 *(Use standard unreduced type. Do not exceed the space provided.)*

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, the study of perinatal infections involves 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. Special studies of specific infections are also in progress including: hepatitis, infectious mononucleosis, pneumonia, varicella-zoster, and condylomata.

The frequency of clinically recognizing infections during pregnancy was determined and geographic variation was demonstrated. Serological tests were used to document certain diseases. The frequency of confirmed clinical cases per 10,000 were: rubella, 8; rubeola, 0.6; mumps, 10; varicella-zoster, 5. The epidemiology and clinical findings associated with infections were studied using serological methods. This has provided data on the frequencies of infections such as cytomegalovirus, herpes simplex, mumps, rubeola, respiratory syncytial virus, and others. The study of abnormal pregnancies and matched controls is in progress using serological techniques. A number of specific studies have been reported on infections including rubella, neonatal meningitis, cytomegalovirus, maternal urinary tract infections, and toxoplasmosis. Further testing is now in progress employing more sophisticated laboratory methods and more complete data analysis.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01-NS-02532-01-ID

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Study of AIDS and SAIDS Neurological Findings and Etiology

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
John L. Sever, Chief, IDB, IRP, NINCDS

COOPERATING UNITS *(if any)*
California Primate Research Center, Davis, CA; Drs. Henry Masur and Abe Macher, Dept. of Critical Care Medicine, CC, NIH

LAB/BRANCH
Infectious Diseases Branch

SECTION
Unit on Clinical Investigations

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
8.3	2.9	5.4

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☒ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Clinical and laboratory studies are conducted to determine the etiological agents and neurological manifestations of acquired immunodeficiency syndrome (AIDS) in man and simian acquired immunodeficiency syndrome (SAIDS) in nonhuman primates. Patients with neurological complications of AIDS are admitted to the Neurology Service of the NIH Clinical Center. Patients admitted to other Institutes are seen by the Infectious Diseases Branch Consultation Service. Patients are evaluated to determine the spectrum of neurological illnesses found in AIDS. Appropriate virological and immunological studies are conducted by IDB and collaborating laboratories.

Studies of nonhuman primates with SAIDS are being conducted simultaneously with our AIDS protocols. Clinical and immunological parameters of SAIDS are being evaluated. Findings are compared to those seen in AIDS patients. Transmission of SAIDS to other primates using tissues from SAIDS monkeys are in progress. Attempts to isolate the etiological agent(s) are being performed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 01985-12-ID

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Viral and Nonviral Antigens or Antibodies in Perinatal and Neurological Diseases

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
PI: David L. Madden, Veterinary Director, IDB, IRP, NINCDS

COOPERATING UNITS *(if any)*
University of California, Los Angeles
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 *(Use standard unreduced type. Do not exceed the space provided.)*

Emphasis has been placed upon development of techniques to improve existing methods of rapid viral diagnosis. The indirect fluorescent assay using the biotin-avidin labeled fluorescein system has continued to be a highly effective method of rapidly screening cultures for herpes antigens. Results are usually obtained within 24-72 hours. Continued efforts to improve the sensitivity of this test are being carried out. The enzyme-linked immunosorbent assay test using the capture technique and employing the biotin-avidin linked alkaline phosphatase system has been developed. Efforts to develop a 4-5 hour test using direct application of this ELISA system to prepared slides and microtiter plates is being evaluated. A new solid phase carrier for the enzyme-linked immunosorbent assay has been developed. These microsticks are machine tooled or molded pegs of plastic or stainless steel. The use of the microsticks permits a wide selection of coating materials and affords greater control and standardization of the solid phase used in the ELISA test. Monoclonal antibodies to varicella zoster have been developed and partially characterized as to serological reactivities and relationship to specific polypeptides and glycoproteins. Flow cytometric studies to measure immunological responses in primates have been continued. Specific monoclonal antibodies to detect the biological function of the lymphocytes of rhesus monkey cells are being developed and characterized. Correlation of commercially available antihuman T and B lymphocyte monoclonal antibodies with functional activity in several primates is being completed. Routine monitoring of tissue cultures for experimental virus studies for mycoplasma contamination continues. Certain remaining aspects of Z01 NS 01984-12 ID are being incorporated into this project.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01-NS-02038-11-ID

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Combined Clinical, Viral and Immunological Studies of Peripheral and CNS Diseases

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Marinos C. Dalakas, Senior 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 *(Use standard unreduced type. Do not exceed the space provided.)*

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 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 polio virus infection or an abnormal immunoregulation and an immune reaction to neuronal cells is under investigation. Abnormalities in lymphocyte subpopulations have been detected in patients with paraproteinemic polyneuropathies; IgM monoclonal band has been identified in the spinal fluid of some of these patients and an abnormal blood-CSF and nerve barrier was found. The metabolic activity of the cortex in ALS patients is being studied using the PET scan and ^{18}F 2-deoxy-D-glucose; hypometabolism was demonstrated not only in the motor but also in the paramotor and sensory cortex, suggesting that ALS is a rather generalized process affecting many cortical regions. Using recombinant DNA alpha$_2$-interferon, an experimental therapeutic trial is being started in ALS patients. Virological studies were performed in patients with Reye's syndrome and their families and their ability to handle a salicylate challenge was investigated.

GPO 895-100

PHS 6040 (Rev. 1/83)

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01-NS-01731-15-ID

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Isolation, Characterization and Diagnosis of Infectious Agents from Chronic Diseases

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Maneth Gravell, Research Microbiologist, IDB, IRP, NINCDS

COOPERATING UNITS *(if any)*
Section on Experimental Pathology, IDB, IRP, NINCDS

LAB/BRANCH
Infectious Diseases Branch

SECTION
Neurovirology Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.8	0.4	1.4

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The variability existing among isolates of Simian hemorrhagic fever (SHF) virus from naturally infected patas monkeys has been studied. Differences were found among isolates in type and severity of disease produced in patas monkeys, cell sensitivity to infection, antigenicity and levels of specific antibody induced. Based on these criteria, isolates have been grouped into 4 strains, 2 of which produce acute infection in patas monkeys (LVR, P-180) and the other persistent infections (P-248, P-741). The P-180 strain induced the most severe disease symptoms in patas monkeys, but infections were rarely fatal. Persistently infected patas monkeys were viremic over a period of years but showed no signs or symptoms of infection. Although none of the 4 strains induced cross neutralizing antibodies, 3 of them (LVR, P-180 and P-741) were antigenically closely related as determined by ELISA. High titers of IgG antibody (31,250 or >) were induced in patas monkeys infected with acute strains of SHF virus, but antibody was barely detectable in persistently infected animals (50 or <). LVR lytically infected MA-104 cells, patas macrophages (MAC) and rhesus MAC. Only patas MAC and rhesus MAC were lytically infected by the P-180 strain, but the persistent strains lytically infected only rhesus MAC. SHF virus had no serological relationship to members of the currently recognized togavirus genera: alpha-, flavi-, pesti-and rubiviruses and, therefore, we have proposed that it be classified as a new genus of togaviruses. In vitro translation studies using LVR strain SHF virus genomic RNA and rabbit reticulocyte lysates have yielded translation product containing 4 polypeptides (40K, 25K, 16K and 12K daltons). These molecular weights correlate with those of structural polypeptides of SHF virions. Immunoprecipitation studies using specific hyperimmune sera and monoclonal antibodies support this conclusion. Our preliminary data, therefore, suggest that virion structural proteins are translated from the complete SHF virus genome, further implying that SHF virus translation more closely resembles that of flaviviruses than alphaviruses.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 01983-12 IDB

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Chronic Viral Infections - Molecular Biology of Human JC Virus

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Eugene O. Major, Special Expert, IDB, IRP, NINCDS

COOPERATING UNITS *(if any)*
Surgical Neurology Branch, NINCDS
University of Illinois at Chicago, Chicago, IL
Microbiological Associates, Bethesda, Maryland

LAB/BRANCH
Infectious Diseases Branch

SECTION
Unit on Microbiology and Genetics

INSTITUTE AND LOCATION
NINCDS, Bethesda, Maryland

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 *(Use standard unreduced type. Do not exceed the space provided.)*

The descriptions of the pathology of virus infections of the CNS are very thorough, but little is known about the interactions which take place between the infecting virus and the neural host cell. The purpose of this research program is to do the molecular investigation of such an infection studying as a model system the human papovavirus, JCV, as it establishes a chronic infection of oligodendroglial cells in the brains of humans described as a progressive multifocal leucoencephalopathy (PML). As a member of the papovavirus family, JCV also has oncogenic potential, being able to induce glioblastomas in both owl and squirrel monkeys. What we have found is that the JCV genome integrates its DNA into the chromosomes of primate glioblastomas in one to several copies and that the integration occurs in discrete regions of the host chromosome perhaps indicating that the development of these types of tumors are cell clonal in nature and not a multicellular participation. We have further determined that the JCV genome produces a gene product responsible for these neoplastic changes, a T protein of 94K daltons. We have detected this protein using a mouse monoclonal antibody to the SV40 T protein which specifically identifies the JC T protein. As a consequence of its expression, the glioblastoma cells secrete plasminogen activator (PA) into their medium unlike normal cells which retain much of their PA inside the cells. We have also determined that cytoskeletal changes of actin fiber disorganization take place as a result of JCV gene expression. To study the control of these genes in more depth, we have cloned them into plasmid vectors using recombinant DNA methods and introduced them into glial cells and other cell types. The 94K, T protein is synthesized in glial cells but a smaller 20K, t protein apparently is not. More importantly a host protein, p53K, which appears to be a regulatory protein both for the cell and viral proteins, does not seem to interact with the JC T proteins but does so with other papovavirus T proteins. We have also made this observation in JC induced glioblastoma cells as well as permissive glial cells.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01-NS-01984-12-ID

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Maternal Infection and Pregnancy Outcome

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
PI: David L. Madden, Veterinary Director, 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:
0	0	0

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

The remaining aspects of this project are being transferred to project # Z01-NS-01985-12-5D.

PHS 6040 (Rev. 1/83) GPO 895-100

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01-NS-02531-02-ID

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Studies in Neuromuscular and CNS Diseases and Their Experimental Models

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Marinos C. Dalakas, Senior Staff Fellow, IDB, IRP, NINCDS

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 *(Use standard unreduced type. Do not exceed the space provided.)*

Enzyme histochemistry in muscle and nerve biopsies is carried out for diagnostic purposes in patients with several neuromuscular disorders. Immunocytochemical studies were 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 (thymosin alpha$_1$, alpha$_7$, beta$_4$) were defined. The interaction between cells of the lymphoid and central nervous system was investigated searching for common antigenic markers on their cell surface. Thymosin beta$_4$, an immunomodulating polypetide, was found to be a common antigen shared by macrophages, dendritic lymphoid cells and oligodendrocytes. 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. The nature of amyloid protein in 15 patients with "sporadic" amyloid polyneuropathy was identified immunocytochemically using specific antibodies to amyloid proteins; the immunocytochemical findings were confirmed biochemically on the extracted amyloid tissue. Immune cellular markers were investigated during evolution of EAN and EAE induced in rhesus monkeys and therapies were attempted using some novel immunomodulating agents. The mechanism of mouse hepatitis virus-induced demyelination was investigated in mice inoculated with mouse hepatitis virus; the distribution of viral antigens was demonstrated in the demyelinated regions.

PHS 6040 (Rev. 1/83)

GPO 895-100

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01-NS-00972-12-ID

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)* Role of Viruses and Other Microorganisms in the Perinatal Period of Experimental Animals

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

William T. London, Veterinary Director, IDB, IRP, NINCDS

COOPERATING UNITS *(if any)*

University of Pittsburgh Presbyterian Hospital, Department of Neuropathology, Pittsburgh, Pennsylvania; Meloy Laboratories, Inc., Springfield, Virginia; Uniformed Services University of the Health Sciences, Bethesda, Maryland

LAB/BRANCH

Infectious Diseases Branch

SECTION

Experimental Pathology Section

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.1	0.3	0.8

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

SV40, a known tumorigenic agent in rodents, was inoculated into humans as a contaminate of killed poliovirus vaccine in the 1950's. The oncogenic and teratogenic properties of this virus were studied in babies of rhesus monkeys, a natural host of SV40 virus. We found that the virus was teratogenic, producing hydrocephalus in several of the inoculated fetal monkeys. Animals were observed for 3 years and at termination of the study, no tumors were found.

Group B streptococci (GBS) are an important cause of serious infection, often neurological, in human neonates. A method for early diagnosis of this in neonates is needed. Using the rhesus monkey model in which fetal monkeys were challenged with GBS, we were able to detect GBS antigen in amniotic or gastric aspirate fluid from all infected monkeys and their newborn by use of the Latex Particle Agglutination (LPA) test. Studies are now under way to use this LPA test to detect human infants at risk with GBS infections.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01-NS-01986-12-ID

PERIOD COVERED
October 1, 1982 through October 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)* Inoculation of Animals with Tissue Culture Grown Materials from Patients with Chronic Neurological Diseases

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
William T. London, Veterinary Director, IDB, IRP, NINCDS

COOPERATING UNITS *(if any)*
Meloy Laboratories, Springfield, Virginia
Microbiological Associates, Bethesda, Maryland

LAB/BRANCH
Infectious Diseases Branch

SECTION
Experimental Pathology Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.4	0.2	1.2

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Delta herpesvirus (DHV) infection in Erythrocebus patas monkeys - A model for human herpes zoster complications: Experimental studies have indicated that patas monkeys become persistently infected with DHV. We are investigating how to activate this persistent infection in the monkey model. We have been unable to activate the persistent infection using immunosuppressive drugs to suppress the monkey's immune system. "Whole body irradiation" may be sufficient to allow reactivation of the DHV.

A group of young cynomolgus Macaca fasiculorus monkeys were monitored for 30 months following intracerebral inoculation of "Biken" strain of measles virus isolated from a human patient with subacute sclerosing panencephalitis (SSPE). The monkeys developed antibodies to measles virus. However, no lesions were found to indicate the virus did any damage to the animal's CNS.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01-NS-02136-09-ID

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)* Control of Acute Infectious Diseases in Experimental Animals Using Biologicals and Chemotherapeutic Agents

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
William T. London, Veterinary Director, IDB, IRP, NINCDS

COOPERATING UNITS *(if any)*
Meloy Laboratories, Springfield, Virginia
Microbiological Associates, Bethesda, Maryland

LAB/BRANCH
Infectious Diseases Branch

SECTION
Experimental Pathology Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.5	0.3	1.2

CHECK APPROPRIATE BOX(ES)
☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Dimethyl sulfoxide, (DMSO) when given intravenously, severely alters the surface markers of lymphocyte-B more than T cells. This was determined by using monoclonal antibodies that identify surface markers on the lymphocytes. Although these changes were severe, they were of short duration. When DMSO was given daily for 15 days, no effect was seen in the clinical course of rhesus monkeys with experimental allergic encephalomyelitis (EAE).

An excellent animal model for the study of human disseminated strongyloidiasis was found and reported. Several spontaneous cases of disseminated strongyloidiasis were observed in our colony of Erythrocebus patas monkeys. The symptoms and lesions, as well as the production of hyperinfective disease in the monkeys are very similar to those in humans with this disease. This, we feel makes the patas monkey an attractive model in which to study this disease.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01-NS-02271-07-ID

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Papovaviruses in Nonhuman Primates

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
William T. London, Veterinary Director, 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 Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
1.1	0.3	0.8

CHECK APPROPRIATE BOX(ES)

☐ (a) Human subjects ☐ (b) Human tissues ☒ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

Twenty-five percent of the monkeys, Aotus trivirgatus 13/52 and Saimiri sciureus 4/15, inoculated intracerebrally with JC virus developed cerebral astrocytomas. The induction period for the tumors was 14 - 30 months following inoculation. The astrocytomas were similar in both species of monkeys. All showed high cellularity, mitotic figures and cellular pleomorphism. JC T antigen antibody titers developed in the inoculated monkeys but did not correlate with tumor production.

ANNUAL REPORT

October 1, 1982 through September 30, 1983

National Institute of Neurological and Communicative Disorders and Stroke

Neuroimmunology Branch

Table of Contents

Annual Report
October 1, 1982 to September 30, 1983
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 the investigation of immune mechanisms operative in neurological diseases. This research includes studies of both experimental animal diseases and human diseases as well as clinical trials of experimental agents and procedures in patients with neurological disorders. Over the past year two major administrative changes have occurred in the NIB which have had a major impact on the activities of the Branch. First, the Branch Laboratories were relocated from Building 36 to the fifth floor of Building 10, adjacent to the Neurology floor for inpatients. Secondly, a unit for the investigation of neuromuscular diseases has been added to the Branch.

The clinical investigations of multiple sclerosis (MS) have been expanded. Considerable effort continues to be focused on the study of monozygotic and dizogotic twins who are either concordant or discordant for the disease. An extensive evaluation of the cell-mediated immune response to viruses, as measured by lymphocyte proliferation, has been completed in 28 twin sets. The responses to mumps and vaccinia were normal. However, an elevated cellular immune response to measles virus was found in seven twins, all of whom have MS. Longitudinal evaluation of this phenomenon has shown that the high response persists for at least five years. Analysis of the cellular immune mechanisms has led to the conclusion that the high response is due to an expansion of measles-specific T cells in the twins with MS.

Immunoglobulin abnormalities in the CSF have also been analyzed in considerable detail in the twin population. Previously it was observed that CSFs from many clinically normal twins of individuals with MS contained either oligoclonal bands or monoclonal bands after electrophoresis. These earlier findings suggested that immunological dysfunction may be occurring in clinically normal individuals, but there were some reservations about this conclusion because the techniques previously employed did not identify the specific proteins in bands and because these studies were performed on concentrated CSF. Over the past year the NIB has developed new methods for the investigation of immunoglobulins in unconcentrated CSF. Proteins are separated by isoelectric focusing and either identified by silver staining or transferred to nitrocellulose paper by electroblotting and identified by immunostaining. Application of these methods to the normal twins has shown that 13 of 15 have immunoglobulins in the CSF which separate into discreet bands. This is consistent with the concept that immunological changes are occurring in the spinal fluid of such individuals. A major question is whether such findings reflect subclinical demyelinating disease. There is serious reason to suspect that this is true, at least in some cases. Over the past year three twins who were originally normal on the basis of clinical evaluation, but who had CSF immunoglobulin bands, have developed definite MS. This observation supports the suspicion that subclinical MS may be more common than previously recognized.

Considerable effort is currently being devoted to trying new therapeutic approaches in MS. A pilot study of lymphocyte depletion has been completed. This showed that repeated lymphocytaphereses which were sufficient to induce lymphopenia did not alter the clinical course in rapidly progressive MS. Important aspects of this study were the evaluation of cellular immune function, immunoglobulin abnormalities in the CSF and lymphocyte subpopulations in the peripheral blood. Even though rather marked lymphopenia was accomplished, significant changes in immune function were not detected. These observations have important implications for the design of future trials in MS.

Within recent years the concept that a defect in immune regulation exists has received wide emphasis. Because of such views, a second therapeutic trial involving the use of an immunomodulator, Poly ICLC, has been initiated in collaboration with investigators at Walter Reed Army Hospital and in the NIAID. Poly ICLC induces the production of interferon and other substances which modify lymphocyte function. However, the administration of this substance is associated with a number of side effects including fever, which can markedly accentuate underlying neurological dysfunction. Consequently considerable effort has been spent developing optimal methods for the administration of Poly ICLC and managing the associated side effects. Progress has been made in these areas and it has been established that the agent can be safely administered to MS patients. The recipients of Poly ICLC produce large amounts of alpha interferon as well as small amounts of gamma interferon. Small amounts of interferon are detectable in the CSF. Profound changes in circulating blood lymphocytes occur within 12-36 hours after the administration of Poly ICLC. Currently eight patients have entered the therapeutic protocol and will be treated for at least one year. Investigations of neuromuscular diseases have expanded. These efforts include the assessment of lymphocyte function in the thymus of patients with myasthenia gravis. Observations to date indicate that thymus lymphocytes of patients with myasthenia gravis differentiate differently than thymus lymphocytes from normal individuals. Patients with recurrent polyneuropathy and familial neuropathy due to amyloidosis are also being studied and currently are participating in experimental therapeutic protocols.

Over the past year Professor Fritz Buchthal has been a Visiting Scientist in the NIB and, in conjunction with a team of investigators, has established an elite electrophysiological laboratory for investigating the many neuromuscular diseases. Within the IRP, NINCDS, and within the entire Clinical Center and the local Greater Metropolitan Area, this unit has become a focus for the evaluation of difficult diagnostic problems. This group has pioneered in the development of new methods for studying tactile stimuli. These are currently being used to investigate patients with sensory neuropathies. In addition, a fourteen lead recording system which will permit wide physiological analysis of muscle fibers has been designed and should be operative within the next year. This approach will enable the evaluation of the normal motor unit and the changes which occur in diseases, such as amyotrophic lateral sclerosis, which affect the motor neuron. Experimental protocols for the investigation of the anatomical and electrophysiological aspects of peripheral nerve abnormalities in Wegner's granulomatosis and in the hypereosinophilic syndrome have been initiated in collaboration with the NIAID.

It is currently believed that cellular immune mechanisms significantly contribute to the production of many human disorders. Consequently major

emphasis has been placed on the investigation of the cellular immune function in man as well as in certain experimental diseases. These studies have been facilitated by recent advances in cell-sorting technology, monoclonal antibodies as well as the production of T cell lines and clones. All these approaches are being broadly applied to research in the NIB. Knowledge about the biology of human immune cells has greatly expanded. It is apparent that the function of immune cells is influenced by components of the major histocompatibility complex (MHC). A number of other molecules on the membrane surface have been identified using monoclonal antibodies. Research in the NIB is directed at delineating mechanisms by which lymphocytes are activated and the function of cell surface molecules in the immune response. The scope of this work will be illustrated by three groups of experiments.

The possible function of the T4 surface molecule of human T cells has been examined in a set of experiments in which cytotoxic lymphocytes (CTL) directed at class I MHC antigens (those specified by HLA A B C Loci) were compared with CTL directed at class II antigens (those specified by DR, SB and DC loci). These studies showed that CTL directed at the SB antigens express the T4 molecule on the membrane surface. Further, treatment of the CTL precursors with monoclonal antibody against the T4 molecule inhibited the expression of CTL function directed at SB antigens. These observations have led to the hypothesis that the T4 molecule recognizes a nonpolymorphic epitope on the class II antigen and serves to focus the CTL to the target site.

In a second set of experiments a measles specific T cell clone derived from a patient with MS has been extensively studied. This clone of lymphocytes expresses T3, T4, and DR molecules on the membrane surface, and when exposed to measles antigen produces IL2. However, these cells only respond when measles antigen is presented in combination with certain specific components of the MHC, namely a specific DR antigen. When presented with antigen in association with other DR specificities, the clone is not activated. Although these observations were obtained from in vitro experiments, it is likely that antigen presentation with DR or other Class II MHC antigens is required for the in vivo activation of T cells, at least those exemplified by the MS measles clone. A third group of experiments has examined the targets of virus-specific CTL. These effector cells express T3 and T8 molecules on the membrane surface and react with virus in association with class I molecules. In collaboration with workers at Harvard Medical School a discreet region one of the class I molecules (HLA-A-2) which controls T cell recognition of influenza-infected targets has been identified.

The studies of human lymphocyte function are being conducted in parallel with the investigation of model diseases in experimental animals. Analysis of the mechanisms responsible for the production of experimental allergic encephalomyelitis (EAE) in mice has been continued. Both acute EAE and adoptively transferred EAE can be induced in SJL mice ($H\text{-}2^S$) by immunization with myelin basic protein. Subsequent experiments have demonstrated that the encephalitogenic portion of the molecule for the SJL mouse resides in the C terminal half (residues 89-169) of the basic protein molecule. Studies completed over the past year have demonstrated that the PL($H\text{-}2^u$) strain of mouse is also susceptible. However, the portion of the basic protein molecule which induces EAE in this strain resides in the first 37 residues of the N terminal portion of the molecule. These observations represent the first demonstration that the

encephalitogenic determinants vary for different inbred strains of a given species. Such findings have important theoretical implications in the consideration of antigenic determinants which might induce cell-mediated autoimmune disease in man. Because man is outbred, a single determinant capable of inducing T cell-mediated CNS disease may not exist.

A second group of findings has resulted from study of EAE produced by the adoptive transfer of sensitized lymphocytes into normal syngeneic recipients. Although the cells responsible for the transfer were previously characterized and shown to belong to a particular set of thymus-derived lymphocytes which are Lyt $1+2^-$, the mechanisms which produce disease in the recipient are not known. One possibility is that the transferred cells directly produce EAE.
An alternative is that the transferred cells induce an immune response in the recipient; this was considered because thymus-derived lymphocytes with inducer function are known to be Lyt $1+2^-$. Recent experiments have demonstrated that the transfer of sensitized lymphocytes into nude mice on an SJL background results in disease which is associated with characteristic pathological abnormalities. Because nude mice lack T cell function, it is unlikely that the transferred cells induced a cellular response in the recipients. Thus these findings provide evidence that transferred immune cells directly produce the demyelinating disease process. In order for transferred cells to produce disease, the sensitized lymphocytes must enter the CNS. The mechanisms responsible for immune cell traffic in the CNS are unknown. The EAE transfer system is currently being used to address this fundamental question. Because the responsible cells are Lyt 1+2- and because this subpopulation of lymphocytes is known to react with antigen in combination with class II MHC molecules, it is believed that such molecules may play an important role in vivo. Such concepts obviously have important implications to the migration of lymphocytes into the CNS of man and to the influence of human MHC upon regulation of this process.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02202-08 NI

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Immunological Studies in Patients with Multiple Sclerosis and Other CNS Diseases

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)

Dale E. McFarlin Chief NI NINCDS

COOPERATING UNITS *(if any)*

ID, NINCDS
NES, ODIR, NINCDS

LAB/BRANCH
Neuroimmunology

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 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 *(Use standard unreduced type. Do not exceed the space provided.)*

Investigation of patients with multiple sclerosis. The general aim of this project is to obtain more precise understanding of multiple factors possibly related either singly or in combination to the pathogenesis of a number of neurological disorders including multiple sclerosis, myasthenia gravis, pyroneuropathy and other neuromuscular diseases. The studies of multiple sclerosis include a detailed evaluation of the histocompatibility makeup and the relationship between immunogenetic background and clinical tissue as well as various immunological parameters including the cellular response to various human viruses. These studies are performed in patients with sporadic disease, patients with a family history of demyelinating disease as well as identical and nonidentical twins who are either concordant or discordant for MS. Cerebrospinal fluid immunoglobulin content and specificity are being evaluated by new highly sensitive techniques. Trials of experimental therapeutic approaches are being conducted in carefully selected patients with multiple sclerosis. Studies of myasthenia gravis are directed at assessment of lymphocyte markers in the blood and thymus. The reactivity of thymocytes and blood lymphocytes to acetylcholine receptor is being evaluated and correlated with antibodies to acetylcholine receptor in the blood. In myasthenia gravis and a wide range of other neuromuscular disorders, detailed electrophysiological evaluation, histopathological studies of muscle and nerve are being conducted in myasthenia gravis and a wide range of other neuromuscular disorders.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02203-08 NI

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

The Immune Response Against Membrane Antigens

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

W. E. Biddison Sr. Staff Fellow NI NINCDS

COOPERATING UNITS *(if any)*

Department of Biochemistry & Molecular Biology, Harvard Medical School
Laboratory of Immunogenics, NIAID, NIH

LAB/BRANCH

Neuroimmunology

SECTION

Neurological Diseases 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 *(Use standard unreduced type. Do not exceed the space provided.)*

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 functions of histocompatibility antigens in forming the target of the immune response and in antigen presentation are being assessed. The studies include evaluation of both class I antigens coded by the HLA-A, B & C loci and class II antigens coded by the DR, SB and DC loci. Monoclonal antibodies to a major surface component are of measles virus, the hemagglutinin, have been produced and are being used to characterize the biosynthesis, glycosylation and insertion of this protein.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02204-08 NI

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)* Immunologic Mechanisms Operative in Experimental Autoimmune Diseases of the Nervous System

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

D. E. McFarlin Chief NI NINCDS

COOPERATING UNITS *(if any)*

Departments of Pathology (Neuropathology) and Neuroscience, Albert Einstein College of Medicine, New York, NY

LAB/BRANCH

Neuroimmunology

SECTION

Neuroimmunology

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 *(Use standard unreduced type. Do not exceed the space provided.)*

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. Immunological and neuropathological studies are being conducted in three forms of the disease: 1) Acute Experimental Allergic Encephalomyelitis, 2) Chronic Relapsing Experimental Allergic Encephalomyelitis and 3) Adoptively Transferred Experimental Allergic Encephalomyelitis. Both the cellular immune response and antibody formation to myelin basic protein and fragments of this substance are being evaluated in genetically defined animals.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02205-08 NI

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Interaction Between Viruses and the Host Immune-System

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Henry F. McFarland, Asst. Chief, NI NINCDS

COOPERATING UNITS *(if any)*

LMB, NINCDS
ID, NINCDS

LAB/BRANCH

Neuroimmunology

SECTION

Cellular Immunology 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 *(Use standard unreduced type. Do not exceed the space provided.)*

The purpose of this study is to examine the host immune response to viruses. The major goal is to examine the normal immune response to naturally occurring viruses in man and to extend these studies to patients in order to identify abnormalities of immune regulation which may be related to the pathogenesis of certain diseases of the nervous system. These studies involve the examination of various T cell subsets and the role of soluble factors, such as IL-2 and interferon in the response to viruses including measles virus. T cell lines and clones are also being used to examine cellular reactivity to these viruses. Studies have also examined the host immune response in experimental infections and are investigating the role of these respones in acute or chronic infections of the nervous system.

ANNUAL REPORT
October 1, 1982 through September 30, 1983

Surgical Neurology Branch
National Institute of Neurological and Communicative Disorders and Stroke

Table of Contents

ANNUAL REPORT
October 1, 1982 through September 30, 1983
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 fifth of the Surgical Neurology Branch beginning October 1, 1982 under the leadership of Dr. Paul Kornblith. The Branch has continued to be 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 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. William Meyer - electron microscopy and enzyme histochemistry (1983)
- Dr. Celia Gately - membrane immunochemistry (1982)
- Dr. Linda Muul - cellular immunology (1982)
- Dr. David Katz - neuropathology and histochemistry (1983)

Senior clinical personnel, in addition to Drs. Kornblith and Smith include:

- Dr. Conrad Kufta
- Dr. Edward Oldfield
- Dr. Donald Wright
- Dr. William Meyer
- Dr. David Katz
- Dr. Thomas Staunton
- Dr. Mary Kay Gumerlock (EOD 8/21/83)

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.

The Clinical Service now has 14 beds on both 5E and 5W as well as operating facilities in Building 10A. More than 120 major neurosurgical cases will be done this year. Clinical admissions are close to 200 per year with consultations for other Institutes at NIH numbering approximately 100/year. Two clinics are functional with more than 800 clinic visits per year. The SNB, through Dr. Katz, 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. Use of the Alkaline Elution and Microtiter Assays for Selection of Chemotherapeutic Drugs for Individual Brain Tumor Patients on the Basis of Their Tumor Cell Drug Sensitivities
   Project No. 83-N-63

10. Intracarotid Chemotherapy Combined with Hemoperfusion of Jugular Venous Blood in the Treatment of Malignant Brain Tumors
    Project No. 83-N-90

Four clinical protocols for brain tumor patients and pursued in collaboration with National Cancer Institute are also in effect:

1. A Phase I Study of Bromodeoxyuridine (NSC 38297) Given by Peripheral Venous Infusion

2. Phase II Trial of AZQ in Patients with Malignant Glioma and Metastatic Brain Tumors

3. Phase I Trial of CBDCA

4. Prospective in vitro Selection of Chemotherapy Agents for Patients with Malignant Brain Tumors

The clinical neurosurgical service includes formal rounds twice a week, a yearly sequence of neuroscience, neuro-oncology, and neurochemistry courses for 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 tumor. The argon laser has been introduced to attempt to improve surgical resection, and has been of value in selected cases. Rapid frozen section glial fibrillary acidic protein and fibronectin staining have been useful in providing more accurate intraoperative neuropathological diagnosis. For radiation therapy, we have completed a study 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 was possible for patients to administer the drug to themselves outside the hospital via special pump devices and new externalized catheter systems. Over 20 patients have received BUdR as adjunct to their radiation therapy. Effective drug levels were achieved although no clear evidence of longer survival has been observed. For clinical chemotherapy we have been able to add three new drugs to the antiglioma armamentarium - AZQ (aziridinylbenzoquinone) and "chocolate" or CBDCA platinum and spirohydantion mustard. AZQ is completing Phase II testing with some 40 patients having received the drug. CBDCA platinum is still in early Phase I testing.

Selective intra-arterial 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 with apparent increase in the bone marrow toxicity of the BCNU. Such elevated BCNU levels should increase overall tumor response to 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. Dr. Oldfield has found that by using an ion exchange cartridge, the majority of the intra-arterial BCNU can be removed. This allows the levels of drug reaching the bone marrow to be significantly decreased. It may allow higher drug levels at tumor cell level with decreased toxicity. So far eight patients have been treated using the new catheter developed by Dr. Doppman. The

procedures are now becoming safer and more rapid. Evaluation of therapeutic results suggests some impressive tumor regressions but more time will be required before a determination of efficacy can be made.

Tumors available for in vitro study now number well over 120 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, Children's Hospital (Washington, D.C.) and a variety of other centers scattered around the country.

Over the period of this report, over one hundred and twenty 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 addition of an argon laser and a cavitron. Metabolic studies of patients with brain tumors have continued. Studies in over 150 patients with positron emission tomographic scanner have shown a relationship between glucose uptake and degree of tumor growth with a clear indication that PET scanning can be helpful in the grading of tumor malignancy.

1. BIOLOGICAL, IMMUNOLOGICAL AND CHEMOTHERAPEUTIC STUDIES IN HUMAN BRAIN TUMORS

A. Biological Characterization and Neuropathological Studies

It has been apparent that the biological factors influencing tumor growth are multifold and include tumor heterogeneity, vascular supply and the intrinsic tumor cell kinetics. 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.

Vascular factors such as the size and distribution of vessels, blood flow rates, and vascular permeability all play a role in the growth of glial tumors. Ultrastructural studies of these vascular factors have proven useful in the understanding of glioma biology.

Cell kinetics and chromosomal patterns have proven to be of import in predicting tumor growth and behavior. Cytofluorometric and flow cytometric techniques have been shown to define the phenotypically characteristic cell populations in specific tumors and have been helpful in understanding the effects of heterogeneity on glioma cell biology.

There are a variety of morphological, cell biological and biochemical parameters which 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 from 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 glioma cells 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. Also, 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 to and differences from this tumor growth to the growth of normal cells.

In order to develop approaches to improving chemotherapy, we have noted 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 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 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 or sensitivity/resistance testing. On the basis of these approaches, we now are in the process of a prospective clinical trial of chemotherapy agent pre-selection.

At the heart of this approach to 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.

In order to overcome the limitation of the aqueous assay in that certain agents one would like to test are of limited or no aqueous solubility, 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 plat (48 wells) takes 40-60 minutes with another 30 minutes required for calculations of cytotoxic indices,

$$C.I. = 1 - \frac{\#\ \text{cells test well}}{\#\ \text{cells control well}}$$

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 we (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	Interferon (glioma)
	CCNU	Interferon (fibroblast)
2.	AZQ	Epidermal Growth Factor (EGF)
3.	Cis-platinum	Fibroblast Growth Factor (FGF)
4.	Spirohydantoin	B-adrenergic agonists
5.	Rapamycin	Butyrate
		Phenytoin
6.	Trans-hydroxy CCNU	A 23187
		5-azacytidine
		hexamethylene bisacetanide

This program involves the individual as will as collaborative work of Drs. J. Bressler, C. Cummins, M. Gately, P. Kornblith, D. Katz and W. Meyer.

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 180 human glioma-derived cell lines for BCNU, 80 such lines for AZQ and some 30 lines for cis-platinum in the microcytotoxicity assays. Fifteen 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 correpondences to the microcytotoxicity assay data. It is of interest that the best correspondence is with cis-platinum. Apparently the direct effects of BCNU on the glioma cell membrane and of AZQ on the mitochondria alter responsiveness in ways other than through DNA effects and thus may have significant anti-tumor

effects even with effects on DNA. 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 in 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 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. Furthermore, it appears that platinum affects glioma cell cytoskeleton.

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.

Flourescence 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.

Immunofluorescence for GFAP had been developed and used on biopsy material. Double immunoflourescence for anti-glial fibrillary acidic protein (anti-GFAP) and for fibronectin has been helpful distinguishing 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. Sterile astrocytomas from surgery were followed with markers for

GFAP and fibronectin through the process of 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.

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. Factor VIII has already been found useful in characterizing cells of vascular origin.

We are currently examining in detail three aspects of the metabolism of gliomas: (1) glucose metabolism: (2) regulation of the expression of protease activity; and (3) chemotherapeutic drug metabolism. A better understanding of these three important aspects of glioma metabolism will allow us to better appreciate the function of normal glia, the interrelationship of neurons and glia, the transition of normal glia to neoplastic glia, and those characteristics that are intrinsic and required for maintenance of the transformed state.

1. Glucose Metabolism

We have shown that there is a close correspondence between the glucose metabolic rates of glioma cell lines in culture and the ^{18}FDG-LCMRglc of the tumors from which they were derived. This suggests that: (a) despite the different techniques used to measure glucose metabolic rate, and despite the different milieux, the physiological properties regulating glucose metabolism is the same *in vitro* and *in situ*; and (b) tissue culture is an excellent model for the *in situ* metabolism of gliomas. Since ^{18}FDG-PET studies have demonstrated a glioma grade-dependent increase in the LCMRglc, which is observed in the culture environment as well, the metabolism of glucose is genotypically altered in the transition of normal glia to glioma.

As is the case for most solid tumors, the glycolytic metabolism of glucose is altered in other ways as well. The levels of high energy reserves (e.g., glycogen, ATP and PCr) are maintained at set-point levels which differ from normal astrocytes. Furthermore, glycolysis is much less efficient than brain; 50% of the glucose taken up is converted to lactate and pyruvate. The glucose oxidative metabolic capacity of gliomas is decreased, and glycolysis therefore is predominantly used to generate the required ATP and PCr. This implies a genotypic lesion in the glycolytic pathway.

The enzymatic activities of the glycolytic pathway have been measured, and high grade glioma-derived cell lines only show increased hexokinase and phosphofructokinase. These are the regulatory enzymes of glycolysis, and enhanced maximum catalytic capacity is consistent with the observed increase

in LCMRglc. ^{18}FDG-PET and tissue culture studies show that low grade gliomas have an LCMRglc intermediate between normal astrocytes and high grade gliomas, and the activities of hexokinase and phosphofructokinase are also intermediate. No other enzyme of glycolysis is altered in a transformation-dependent manner in high or low grade gliomas.

Increased flux into pentose phosphate pathway is also a hallmark of solid tumor metabolism. The flux through this pathway is enhanced in a grade-dependent manner in glioma-derived cell lines and in high grade glioma specimens derived from the OR. The regulatory enzyme for this pathway is glucose-6-phosphate dehydrogenase, and despite the apparent increased flux, the activity of this enzyme in high grade glioma-derived cell lines is only 10% of the activity found in normal astrocytes. This glucose-6-phosphate dehydrogenase of normal astrocytes is significantly inhibited by NADPH, but the glucose-6-phosphate dehydrogenase of gliomas is remarkably insensitive. This suggests that gliomas have an altered isozyme, and studies to determine this are underway.

The blood-brain barrier is commonly altered in gliomas, implying that these tumors may metabolize a wider range of carbon compounds than normal astrocytes. The metabolism of exogenously supplied glutamate and glutamine is rather low in surgical samples of normal cortex, but is enhanced in glioma tissue obtained from the OR. Glioma-derived cell lines also have significantly increased oxidative metabolism for glutamate and glutamine.

Taken together, these results demonstrate that the glucose metabolism of tumors is altered in three fundamental ways (1) glucose uptake is increased, to maintain glycogen, ATP and PCr largely by anaerobic glycolysis; (2) the pentose phosphate pathway flux is elevated, largely due to the alteration in the control features of the regulatory enzyme, glucose-6-phosphate dehydrogenase; and (3) greater reliance is placed on the oxidative (and thus energy yielding) metabolism of alternative fuels, such as amino acids.

2. Regulation of the expression of proteases and modification of the extracellular space.

Glioma invasiveness is primarily a function of this tumor's ability to alter the surrounding microenvironment. We have demonstrated that gliomas express and secrete plasminogen activator, and a large number of other proteases. In addition, certain other brain tumors secrete plasmin inhibitors, which block host-defense proteolysis. Lastly, high grade rapidly dividing gliomas are associated with increased plasma levels of the cellular binding protein, fibronectin.

A very sensitive technique was developed in this laboratory for the demonstration of plasminogen activator (PA) activity. This technique allows us to reliably and rapidly measure the PA activity in as little as 50 ug of cell protein (approximately 10^4 cells). Using this technique, we have been able to demonstrate that expression and secretion of PA activity is common feature of high grade glioma-derived cell lines. Normal astrocyte cell cultures do not synthesize or secrete PA. Since this enzyme has been correlated with transformation, dedifferentiation and invasiveness in other cellular systems, we hypothesized that inhibition of growth or differentiation

may result in decreased PA secretion. This is in fact the case for most glioma lines: agents which alter the differentiation state, or decrease the growth rate decrease the expression of PA. The mechanism of this effect is currently the subject of active experimental interest. Differentiating agents appear to block the de novo synthesis of PA. At the present time, other hypothesized mechanisms for decreased PA production (such as active synthesis of a PA inhibitor) appear not to function in glioma-derived cell lines.

In collaboration with Dr. Eugene Major (IDB/NINCDS) we have begun a series of studies to elucidate the molecular basis for PA expression in JC virus-induced monkey gliomas. To date, cell lines which have the complete JC virus genome have been shown to synthesize and secrete PA. The presence of the T antigen, but not the small T antigen is required for PA production in monkey glioblastomas in vitro. Normal monkey cortical cultures do not secrete PA activity.

PA is only one of many potential proteinases which could play a role in tumor invasiveness. Chordomas are a rare tumor, but one which is characterized by invasiveness, since this notochordal remnant tumor will slowly erode bone, cartilage and a variety of other tissues. In collaboration with Dr. Bernadette Tyree (L DBA/NIDR), we are currently investigating the collagenases of chordomas. The milk protein, casein, is widely used as a substrate for the assay of proteinases. Glioma tissue, and normal cortex did not show caseinolytic activity, but the activity was significantly enhanced in chordoma tissue. Amino acids, covalently attached to carbobenzoxyl blocking groups, and conjugated with nitrophenol or nitroanilide are widely used to assay proteinases. We have applied a variety of these substrates to determine the proteinases in normal hair cortex, glioma tissue, and chordoma. For most substrates, activity is seen in homogenates of all three tissues, but the activity is extensive in chordomas, low in cortex, and intermediate in gliomas. We are in the process of identifying particular proteinase activities.

Proteases have many roles in the physiological function, such as clot formation, clot lysis, and host-defense mechanisms against tumor invasiveness. We recently examined in detail the plasmin inhibitory activity in two meningiomas, one glioma, and one sarcoma. Of the two meningiomas, one was temporal in location, and the other was extensive in size, completely occluding the sagittal sinuses. Extracts of the meningioma showed no plasmin inhibition, but the inhibitory activity was extensive in the tumor. This implies that plasmin inhibitor activity can be expressed in tumors to block host defense mechanism. Thromboembolic complications are not infrequent in patients with glioblastoma. The tissue from one glioma, removed from a individual with thromboembolic complication, was also shown to express significant levels of plasmin inhibitor. This yields some insight into the possible range of tumor-host interaction, and may explain the thromboembolysis seen in certain glioma patients.

Fibronectin (Fn) is a protein which is widely synthesized as a cellular binding protein, and high levels have been implicated in disseminated intravascular coagulopathies. Patients with various neurological disease, non-CNS solid tumors, low grade astrocytomas, or growth-arrested glioblastomas show blood Fn levels with the normal range. However, patients who have

actively growing high grade gliomas have a mean Fn about twofold greater than normal volunteers. This observation has significance in its predictive value, and in a better understanding of the range of tumor interactions.

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* microcytyotoxicity 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 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 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 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 tenfold 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 40 patients (with recurrent malignant gliomas and failure to respond to radiation therapy and other chemotherapy), we have achieved a 35% 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 18 months. Our data parallel that of the Mayo Clinic, the M.D. Anderson Hospital and University of Maryland.

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 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 dimethylfomamide (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 Chemotherapy Agents for Patients with Malignant Brain Tumors" is now in effect 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 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 Services. 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 ability to study 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. To evaluate the effects of chemotherapeutic agents on glial cell metabolism, a study of cultured glioma cells treated with chemotherapy has been accomplished. The drug bischloroethylnitrosourea (BCNU), a nitrogen mustard, is a relatively effective drug for the chemotherapy of gliomas. Microcytotoxicity assays have shown that in culture, some glioma-derived lines are sensitive to BCNU and other lines are not. The in vitro determination of sensitive/resistant appears to predict the efficacy of BCNU treatment in patients. The mechanism of action of BCNU is still unclear; but several lines of evidence suggest a target in addition to DNA:

(1) the BCNU-mediated killing is rapid for DNA damage alone; (2) BCNU is a rather poor DNA crosslinker; (3) other nitrogen mustards which alkylate DNA have a much longer killing time.

BCNU has recently been reported to specifically and irreversibly inhibit the enzyme glutathione reductase. This is a potentially explanatory concept, since it suggests that the BCNU mediated killing is a result of peroxide-free radical damage, a process consistent with the observed time course. Furthermore, it predicts the following:

(1) Sensitive/resistant glioma lines differ in the rate of free radical/peroxide production; (2) Sensitive/resistant glioma lines differ in the mechanism of free radical/peroxide detoxification; (3) Sensitive/resistant glioma lines differ in the possible targets attacked by free radicals/peroxide and/or (4) The glutathione reductase of sensitive/resistant cell lines may be reflected in a relative sensitivity toward irreversible inhibition by BCNU.

The activities of glutathione peroxidase and glutathione reductase, and the concentrations of reduced (GSH) and oxidized (GSSG) glutathione have been measured in selected typical sensitive and resistant cell lines (as determined by the microcytotoxicity assay). The levels of GSH and GSSG are about fourfold higher in the resistant cell lines that in the sensitive lines. The activity of glutathione peroxidase is not different between the sensitive and resistant cell lines, and this enzyme is not affected by BCNU treatment.

The activities of glutathione reductase are higher in the resistant cell lines than in the sensitive, and after BCNU treatment, this enzyme is inhibited to approximately the same degree in both sensitive and resistant cell lines. Greater residual activity is seen, however, in the resistant lines.

If the response to BCNU is mediated by inhibition of the glutathione system, modulation of endogenous levels of GSH/GSSG should alter the effect of BCNU. Studies are currently underway to test this hypothesis. Sulfoximines decrease the GSH/GSSG levels in resistant cell lines, and we will soon test the consequent effect on BCNU-mediated cell killing.

If BCNU-sensitive cell lines differ from resistant lines due to enhanced free radical/peroxide production, treatment with free radical scavengers, or lipid peroxide blockers should block the BCNU killing. These experiments are in progress.

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.

In a potentially major new observation we have noted that there are "new" proteins demonstrable on SDS polyacrilamide gel electrophoresis after glioma cells are treated with cAMP or DMF. These "new" proteins may represent antigens induced by the differentiation agents. These proteins may possibly account for the changes in microcytotoxicity response which have been seen. It will now require two dimensional gel electrophoresis with isoelectric focussing to further identify these proteins. When these proteins are isolated, we can immunoprecipitate them and determine how they relate to the immunological responses.

Work during the past year has continued to be directed at gaining a better understanding of the mechanisms by which gliomas escape cellular immune attack. One such mechanism involves a defect in immunogenicity which can be overcome by "help" provided by soluble factors released by peripheral blood mononuclear cells in mixed lymphocyte reactions. Attempts to define the nature of this factor, as well as to elicit autologous tumor-specific responses by its use, have been hampered by the ability of mixed lymphocyte culture supernatants to elicit nonspecific "natural killer-like" cytolytic effectors in addition to augmenting specific cytolytic lymphocyte responses. Therefore several reagents were screened for their ability to inhibit the generation or action of nonspecific effectors while permitting specific cytolytic lymphocyte responses to proceed unimpeded. One such substance was identified. Hydrocortisone at concentrations of 10^{-6} M to 5 X 10^{-5} M was found to inhibit the generation of nonspecific effectors by greater than 90% while having little or no effect on specific cytolytic lymphocyte responses. The inclusion of this reagent in mixed lymphoycte-tumor cultures should thus greatly facilitate further studies on factors affecting the immunogenicity of gliomas as well as attempts to elicit autologous glioma-specific cytolytic lymphocyte responses in vitro.

A second mechanism by which glioma cells escape cellular immune attack is by the production of mucopolysaccharide cell coats. The secretion of large cell coats is stimulated by the interaction of glioma cells with a nondialyzable factor produced by some component of the blood mononuclear cell population. Initial studies suggest that T3-negative adherent cells, possibly monocytes, may be responsible for the production of this factor. Coat formation has been quantitated by use of a Bausch and Lomb image analysis system and by means of ELISA assay in which hyaluronic acid is quantitated by measuring its interaction with the hyaluronic acid-binding region of a proteoglycan from rat chondrosarcoma cells. Preliminary results with the ELISA assay have suggested that interaction of glioma cells with the blood mononuclear cell-derived factor does not increase the amount of soluble hyaluronic acid which glioma cells secrete into the culture medium but rather increases the fraction of secreted hyaluronic acid which is held in cell surface-associated form. However, problems with standardization and reproducibility of the ELISA assay have been encountered, and attempts to refine and improve this assay are in progress.

A third mechanism by which glioma cells may escape cellular immune attack is through the secretion of soluble immunosuppressive factors. It was previously reported by other laboratories that some glioma patients possessed nonspecific immunosuppressive substances in their plasma. We have obtained similar results with plasma from some of our glioma patients. The immunosuppressive substance in patients' plasma was eluted from a gel filtration column in the same fractions as marker proteins of 60,000-80,000 molecular weight. In contrast, immunosuppressive substances released by glioma cells*in vitro* eluted in the void volume of S-200 columns, implying a molecular weight equal to or greater than 200,000. Thus the immunosuppressive substance present in patients' plasma *in vivo* is not identical to that produced by glioma cells *in vitro*; however it cannot be excluded that the larger factor produced *in vitro* is a precursor of the smaller factor observed *in vivo*. Further biochemical characterization of these factors is in progress.

D. PET Scanning

Another area of significant accomplishment for the Branch has been the development of a positron emissiom 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 threefold 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 to 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.

E. Animal Model (RT9) Tumor Studies for Evaluation of Tumor Blood Flow, Blood-Tumor Transport and Drug Delivery

Three injected intracerebral animal models are under study (RT-9, C-6, RG-2 rat model). Quantitative autoradiographic techniques are utilized for study of cerebral blood flow, capillary permeability, blood-brain transport (flux) and glucose utilization. These studies address the direct pathophysiologic mechanisms underlying the disease process as well as secondary effects (vasogenic edemas). In addition, a physical method for producing vasogenic edemas is used (free lesion), and is compared with tumor-induced changes in brain surrounding the injected tumor.

Radioisotopes used in these studies include ^{14}C-Aminoisobutyric acid, 2-deoxyglucose, ^{125}I- and ^{131}Iodine labelled compounds, (i.e., RISA), ^{14}C-Iodoantipyrine, ^{14}C-misonidazole.

QAR technique allows determination of local tissue regions of very small volumes (100-200 cells) which can be rapidly assayed, digitized and manipulated on an image array processor.

2. BIOLOGICAL STUDIES OF HUMAN PITUITARY TUMORS RESEARCH EFFORTS CONCERNED WITH THE BIOLOGICAL ACTIVITIES OF PITUITARY TUMORS INCLUDE BOTH CLINICAL AND IN VITRO STUDIES.

A. Clinical

During the past year we have completed the following clinical studies of patients with pituitary adenomas.

1. Shown that the ACTH secretion of the adenomas of Cushing's disease and Nelson's Syndrome is stimulated by corticotropin releasing factor (CRF), the hypothalamic hormone which regulates the ACTH secretion of the normal gland. This implies that these tumors have receptors for this hormone and that receptor-directed therapy may be beneficial.

2. Shown that CRF stimulation tests distinguish those patients with Cushing's Syndrome who have pituitary tumors from patients with ectopic ACTH secretion and adrenal tumors. This has been a difficult differential diagnosis in the past.

3. Shown that metabolic clearance rate of CRF in Cushing's disease and Nelson's Syndrome is similar to normal controls.

4. Established that glucocorticoids inhibit CRF-stimulated ACTH secretion in Nelson's Syndrome.

5. Shown that the growth hormone secretion of the tumors of acromegaly is stimulated by growth hormone releasing factor, a recently discovered hypothalamic hormone.

The above-mentioned studies were performed in collaboration with Developmental Endocrinology Branch, NICHD.

6. Shown that bilateral petrosal sinus sampling in the diagnostic evaluation of Cushing's Syndrome. Previously unilateral sampling had been considered sufficient.

7. Shown that bilateral inferior petrosal sinus sampling will allow localization of the side of the pituitary gland in which ACTH-secreting microadenomas reside. Our surgical success has been 100% in seven patients with Cushing's disease since the institution of this preoperative study.

8. By administering CRF during inferior petrosal sinus sampling demonstrated that it is the pituitary adenoma responding to CRF in Cushing's disease and not the normal pituitary gland.

The above studies were performed collaboratively with the Diagnostic Radiology Department, Clinical Center, and Developmental Endocrinology Branch, NICHD.

B. Basic Research in Laboratory Animals

1. Demonstrated that CRF is actively cleared from the ventricular CSF of monkeys. This supports previous work implicating a physiological role of the CSF in the distribution of neurohormones in the CNS.

2. Shown that intraventricular CRF stimulates pituitary ACTH secretion in doses smaller than those required for pituitary activation by intravenous administration. This suggests a mechanism of active delivery of CRF to the pituitary gland.

C. In vitro

Work in this area continues to be encumbered by the loss of hormone secretion in these tumors after a few weeks in culture. We continue our efforts to develop culture methods to overcome this characteristic if these tumors and our search for stable lines. The stimulatory effect of CRF and GRF on the hormonal secretion and proliferative activity of the tumors is being evaluated in vitro and also being compared with in vivo stimulation tests.

The recent isolation synthesis of the hypothalamic releasing factors for ACTH and GH allows us to use these tools to investigate the hormonal secretory mechanisms of the tumors of Cushing's disease, Nelson's Syndrome and acromegaly.

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] fluorodeoxglucose (FDG), represents a totally new approach to the understanding of pathophysiology of many neurological diseases. This method provides physiological information not available with any other imaging procedure.

During the past year we have:

a) Obtained and analyzed data with the FDG-PET technique in a large number of patients (over 140 cases at the last count) harboring CNS tumors. These data clearly indicate that the FDG-PET technique is a powerful research tool to obtain information on some metabolic features as well as new diagnostic and basic insights about these lesions;

b) Initiated scanning with the NEURO-PET, a new high resolution-high sensitivity PET tomograph developed in our section. We have already scanned, with superb results, more than 100 patients;

c) Obtained the first (FDG-PET) in vivo metabolic values for the normal and abnormal brain stem and spinal cord;

d) Provided the indispensable theoretical and technical expertise for FDG-PET projects by other NINCDS branches. These projects deal with epilepsy, Alzheimer's disease, dyskinesias, Parkinson's disease, ALS and Tourette syndrome.

The Neuroradiology and Computed Tomography Section is also involved in the following other research projects:

Transmission Computed Tomography (CT). Our work has continued with 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 tumor 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 digital subtraction angiography (DSA) studies of the spine in cases of arteriovenous malformation and tumors of the spinal cord have been successful. DSA is a valuable screening and follow-up technique for the evaluation of certain vascular conditions of the spinal cord.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02367-05 SN

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Biological, Immunological and Chemotherapeutic Studies of Human Brain Tumors

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Paul L. Kornblith, Chief, Surgical Neurology Branch, NINCDS (Cont'd) OTHER*

COOPERATING UNITS *(if any)*

Radiation Oncology, NIC; Medical Oncology, NCI; BEIB, DRS, NIH

LAB/BRANCH

Surgical Neurology Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
6.0	5.0	1.0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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 glycoprotein 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.

- - - - - - - -

* OTHER

Maurice Gately	Senior Staff Fellow	SN NINCDS
Paul McKeever	Medical Officer	SN NINCDS
Craig Cummins	Staff Fellow	SN NINCDS
Joseph Bressler	Senior Staff Fellow	SN NINCDS
Conrad Kufta	Senior Staff Fellow	SN NINCDS
Edward Oldfield	Senior Staff Fellow	SN NINCDS
David Katz	Senior Staff Fellow	SN NINCDS
William Meyer	Special Expert	SN NINCDS

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02454-03-SN

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Biological Studies of Human Pituitary Tumors

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)

(Cont'd) OTHER*

Edward H. Oldfield, Senior Staff Fellow, Surgical Neurology Branch, NINCDS

COOPERATING UNITS *(if any)*
Developmental Endocrinology Branch, NICHD, Diagnostic Radiology, CC

LAB/BRANCH
Surgical Neurology Branch

SECTION
Office of the Chief

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 *(Use standard unreduced type. Do not exceed the space provided.)*

The influence of the hypothalamic releasing factors CRF and GRF on the hormonal secretion of pituitary adenomas has been determined in vitro and correlated with the patients' response in vivo. These studies indicate that the pituitary tumors causing Cushing's disease, Nelson's Syndrome and acromegaly are responsive to their appropriate releasing factor. We are also investigating the influence of the releasing factors on the rate of growth of pituitary tumors in vitro. By understanding the mechanism of the secretory responses of these tumors to the releasing factors, new therapeutic methods may evolve.

- - - - - - - - -

*OTHER

Paul E. McKeever	Medical Officer	SN NINCDS
Paul L. Kornblith	Chief	SN NINCDS
Craig Cummins	Staff Fellow	SN NINCDS

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 01195-19 SN

PERIOD COVERED
October 1, 1983 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Radiographic and Radioisotopic Angiography of the Spinal Cord

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation) Chief, Neuroradiology and
(Cont'd) OTHER* G. Di Chiro, Computed Tomography Section SN NINCDS

COOPERATING UNITS *(if any)* Diagnostic radiology and Nuclear Medicine Departments, Clinical Center, NIH; Medical Examiner's Office, Department of Public Health, Philadelphia, PA

LAB/BRANCH
Surgical Neurology Branch

SECTION
Neuroradiology and Computed Tomography Section

INSTITUTE AND LOCATION
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 *(Use standard unreduced type. Do not exceed the space provided.)*

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 indicates that these methods are useful, and indeed excellent screening and follow-up procedures in the evaluation of certain vascular lesions of the spinal cord.

*OTHER

J.L. Doppman	Chief	DR CC
P.L. Kornblith	Chief	SN NINCDS
E.H. Oldfield	Senior Staff Physician	SN NINCDS
A.E. Jones	Associate Chief	SN NINCDS

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02073-10 SN

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Computed Tomography (Transmission) and Nuclear Magnetic Resonance (NMR)

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation) G. Di Chiro Chief, Neuroradiology and Computed Tomography Section SN NINCDS
(Cont'd)OTHER *

COOPERATING UNITS *(if any)* Diagnostic Radiology, Nuclear Medicine Department, CC, NIH; Infectious Diseases Branch, IRP, NINCDS, NIH; Physics Department, Tufts University, Boston, 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 *(Use standard unreduced type. Do not exceed the space provided.)*

Computed Tomography (CT) in its transmission, emission and soon Nuclear Magnetic Resonance (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 use protons instead of x-rays.

*OTHER

PI:	R.A. Brooks	Staff Physicist	SN NINCDS
	V.J. Sank	Expert	DR CC
Other:	P.L. Kornblith	Chief	SN NINCDS
	B.H. Smith	Deputy	SN NINCDS
	A.M. Cormack	Physicist	Tufts University
	J.L. Sever	Chief	ID NINCDS
	W.T. London	Chief, Experimental Pathology Section	ID NINCDS

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02315-06 SN

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Positron Emission Tomography

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
(Cont'd) OTHER* G. Di Chiro Chief, Neuroradiology and Computed Tomography Section SN NINCDS

COOPERATING UNITS *(if any)* BEIB, DRS, NIH; Naval Res. Lab., Wash., DC; Lab of Cerebral Metabolism, NIMH, NIH; ODIR, NINCDS; EB, NINCDS; ETB, NINCDS; LCP, NCI; Brookhaven National Lab., Upton, NY; Div. of Nucl. Med., Dept. of Rad. Science, UCLA, Los Angeles, CA

LAB/BRANCH
Surgical Neurology Branch

SECTION
Neuroradiology and Computed Tomography Section

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
3.5	3.5	0

CHECK APPROPRIATE BOX(ES)

[X] (a) Human subjects [ ] (b) Human tissues [ ] (c) Neither
[X] (a1) Minors
[ ] (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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 intracranical cavities). The unique property of PET is that it provides physiologic information not available with any other imaging procedure.

Since June 1982 we have been using the new high-resolution, high-sensitivity scanner built in our section, the Neuro-PET. The performance of this scanner has exceeded all our expectations. This is, at present, the best PET-tomograph in the world and already has allowed new applications of the PET technique.

*OTHER	A.G. Blasberg	Medical Officer	LCP NCI
	A.P. Wolf	Senior Chemist	Brookhaven
	R.A. Brooks	Staff Physicist	SN NINCDS
	L. Mansi	Expert	SN NINCDS
	D. Bairamian	Guest Worker	SN NINCDS
	N.J. Patronas	Staff Physician	DR CC
	P.L. Kornblith	Chief	SN NINCDS
	B.H. Smith	Deputy Chief	SN NINCDS
	M. Dalakas	Senior Staff Fellow	ID NINCDS
	W.H. Theodore	Neurologist	EB NINCDS
	T.N. Chase	Chief	ETB NINCDS
	A.E. Jones	Associate Chief	SN NINCDS
	R.M. Kessler	Staff Physician	CC NM
	R. Margolin	Staff Physician	CC NM
	L. Sokoloff	Chief	LCM NIMH
	D.E. Kuhl		UCLA
	M.E. Phelps		UCLA

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 NS 02560-02 SN*

PERIOD COVERED
October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Evoked Potential Correlates of Neurological Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*
(Name, title, laboratory, and institute affiliation)
Barry H. Smith, Deputy Chief, Surgical Neurology Branch, NINCDS (Cont'd) OTHER*

COOPERATING UNITS *(if any)*
Communicative Disorders Program; Clinical Neurosciences Branch, IRP; Developmental and Metabolic Neurology Branch, IRP

LAB/BRANCH
Surgical Neurology Branch

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NINCDS, NIH, Bethesda, Maryland 20205

TOTAL MANYEARS:	PROFESSIONAL:	OTHER:
0.4	0.4	0

CHECK APPROPRIATE BOX(ES)

☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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.

This project has been discontinued due to the departure of Dr. Barry H. Smith from the National Institutes of Health.

- - - - - - -

*OTHER:

Ernest J. Moore	Staff Scientist	CDP NINCDS
Dan Stowens	Staff Fellow	DMNB NINCDS
Susumu Sato	Neurologist	EB, CDNDP NINCDS

*This project was transferred from the Communicative Disorders Program to the Surgical Neurology Branch, IRP.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 NS 02010-11 SN

PERIOD COVERED

October 1, 1982 through September 30, 1983

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*

Neurophysiological Mechanisms of Pain

PRINCIPAL INVESTIGATOR *(List other professional personnel on subsequent pages.)*

(Name, title, laboratory, and institute affiliation)

Choh-Luh Li, Medical Officer, Surgical Neurology Branch, NINCDS

COOPERATING UNITS *(if any)*

LAB/BRANCH

Surgical Neurology Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NINCDS, NIH, Bethesda, MD 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 *(Use standard unreduced type. Do not exceed the space provided.)*

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 rat 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.

This project has been discontinued due to the departure of Dr. Li.

☆ U.S. GOVERNMENT PRINTING OFFICE: 1984-421-132:4638