DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00471-31 LPP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Studies of Heredity and Environment in Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Allan F. Mirsky, Ph.D. Chief LPP, NIMH

COOPERATING UNITS *(if any)*

Institute for Research on Kibbutz Education, Haifa University, Israel; Hebrew University, Israel; Oranim Teacher's College, Israel; Bar Ilan University, Israel; University of Chicago, Illinois; William Beaumont Hospital, Michigan

LAB/BRANCH

Laboratory of Psychology and Psychopathology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

This project has been composed of the following studies: (1) An intensive multi-disciplinary study of a family with MZ quadruplets (daughters) concordant as to schizophrenia but discordant as to severity and outcome; (2) Studies of Danish adoptees and their biological and adoptive families; (3) A study of children (of schizophrenic and control parents) reared in town or kibbutz in Israel. We maintain contact with the quadruplets but have not pursued active studies with them during the past two years. The Danish adoptees are of continuing interest to us and we are preparing additional reports on factors involved in their psychiatric outcome. The Israeli children are the subject of intensive research efforts and we are planning further behavioral and biological studies with them.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

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PI: Allan F. Mirsky, Ph.D. Chief LPP, NIMH

COOPERATING UNITS *(if any)*

Institute for Research on Kibbutz Education, Haifa University, Israel; Hebrew University, Israel; Oranim Teacher's College, Israel; Bar Ilan University, Israel; University of Chicago, Illinois; William Beaumont Hospital, Michigan

LAB/BRANCH

Laboratory of Psychology and Psychopathology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

This project has been composed of the following studies: (1) An intensive multi-disciplinary study of a family with MZ quadruplets (daughters) concordant as to schizophrenia but discordant as to severity and outcome; (2) Studies of Danish adoptees and their biological and adoptive families; (3) A study of children (of schizophrenic and control parents) reared in town or kibbutz in Israel. We maintain contact with the quadruplets but have not pursued active studies with them during the past two years. The Danish adoptees are of continuing interest to us and we are preparing additional reports on factors involved in their psychiatric outcome. The Israeli children are the subject of intensive research efforts and we are planning further behavioral and biological studies with them.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00484-26 LPP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Psychophysiological Responsivity and Behavior in Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Theodore P. Zahn, Ph.D. Research Psychologist LPP, NIMH

COOPERATING UNITS *(if any)*

Laboratory of Socio-Environmental Studies, Child Psychiatry Branch, Laboratory of Clinical Science, Neuroscience Branch, Biological Psychiatry Branch, and Clinical Neurogenetics Branch, NIMH; Hypertension-Endocrine Branch, NHLBI.

LAB/BRANCH

Laboratory of Psychology and Psychopathology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.7	0.8	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 general purpose of this project is to investigate the roles of autonomic nervous system (ANS) activity, attention, and information processing and their interrelationships in the pathology, etiology, and prognosis of psychiatric disorders. A second purpose is to determine biological and psychological processes related to ANS activity and attention. ANS activity is assessed by peripheral measures, such as skin conductance, heart rate, and skin temperature. Subjects are tested under conditions of rest, presentation of tones, and performance on tasks such as reaction time and mental arithmetic.

Biological mechanisms are investigated by correlating these variables with enzyme activity, neuropeptides, and levels of biogenic amines and their metabolites.

Studies are being done on unmedicated patients with diagnoses of schizophrenia, affective disorder, obsessive compulsive disorder, anxiety-panic disorder, and autism to test the diagnostic specificity of patterns of ANS activity. Effects of state changes are studied in cases of multiple personality, as well as with brain dysfunction as revealed by CT and PET scans. In some studies blood samples are taken during ANS recording sessions in which stressful procedures are given. In one, the effects of success and failure to escape an aversive noise are assessed, and in another, the effects of a dose of yohimbine is being studied. Clinical trials of various treatments are studied. These include pimozide, propranolol, verapamil, and hemodialysis in schizophrenia, clorgyline and clomipramine in obsessives, and alprazolam and imipramine in panic-anxiety patients.

Psychological correlates are studied via clinical background data, clinical ratings and questionnaires, and by procedural variations. The use of confirmatory factor analysis in data reduction and to improve quantification of ANS activity is being explored.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00484-26 LPP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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Psychophysiological Responsivity and Behavior in Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Theodore P. Zahn, Ph.D. Research Psychologist LPP, NIMH

COOPERATING UNITS *(if any)*

Laboratory of Socio-Environmental Studies, Child Psychiatry Branch, Laboratory of Clinical Science, Neuroscience Branch, Biological Psychiatry Branch, and Clinical Neurogenetics Branch, NIMH; Hypertension-Endocrine Branch, NHLBI.

LAB/BRANCH

Laboratory of Psychology and Psychopathology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.7	0.8	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.)*

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Psychological correlates are studied via clinical background data, clinical ratings and questionnaires, and by procedural variations. The use of confirmatory factor analysis in data reduction and to improve quantification of ANS activity is being explored.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 00486-14 LPP

PERIOD COVERED: October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Psychophysiological Effects of Stimulant Drugs in Children

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Theodore P. Zahn, Ph.D.	Research Psychologist	LPP, DIRP, NIMH
Other:	Judith Rapoport, M.D.	Chief	CHP, NIMH
	Martine Flament, M.D.	Guest Researcher	CHP, NIMH
	Marcus Kruesi, M.D.	Clinical Associate	CHP, NIMH

COOPERATING UNITS *(if any)*: Child Psychiatry Branch, NIMH

LAB/BRANCH: Laboratory of Psychology and Psychopathology

SECTION:

INSTITUTE AND LOCATION: NIMH/ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.3	0.2	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.)*

Tests of the effects of acute and chronic administration of caffeine on autonomic nervous system (ANS) functioning have been carried out to evaluate the role of ANS activity in behavioral and subjective effects of this drug. A test of attention using a reaction time method is included.

The test protocol involves recording peripheral indicators of ANS activity such as skin conductance (SC), heart rate (HR), and skin temperature during a session consisting of a rest period, presentation of a series of simple tones to which no response is required, and the reaction time task. Studies have been carried out on the effects of the acute administration of two doses of caffeine and a placebo in 6-13 year old boys and in men, and a study of chronic (2 week) caffeine intake in children.

The effects of both acute and chronic administration of caffeine were increases in SC indices of arousal but some trends toward decreases in HR. The SC results are consistent with the hypothesis that caffeine can be considered a pharmacologic model for anxiety, but the HR effects suggest the model is imperfect.

In a current study, an acute dose protocol with caffeine is being conducted on children with anxiety disorders and controls. This will test the hypothesis, for which there is evidence in adults, that patients with anxiety disorders are more sensitive to caffeine than controls.

Another current study compares ANS activity and attention in boys with diagnoses of Conduct Disorder and Attention Deficit Disorder.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00486-14 LPP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

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PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Theodore P. Zahn, Ph.D.	Research Psychologist	LPP, DIRP, NIMH
Other:	Judith Rapoport, M.D.	Chief	CHP, NIMH
	Martine Flament, M.D.	Guest Researcher	CHP, NIMH
	Marcus Kruesi, M.D.	Clinical Associate	CHP, NIMH

COOPERATING UNITS *(if any)*

Child Psychiatry Branch, NIMH

LAB/BRANCH

Laboratory of Psychology and Psychopathology

SECTION

INSTITUTE AND LOCATION

NIMH/ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.3	0.2	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.)*

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In a current study, an acute dose protocol with caffeine is being conducted on children with anxiety disorders and controls. This will test the hypothesis, for which there is evidence in adults, that patients with anxiety disorders are more sensitive to caffeine than controls.

Another current study compares ANS activity and attention in boys with diagnoses of Conduct Disorder and Attention Deficit Disorder.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00491-10 LPP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Personality Factors and Psychophysiological Responses to Changing Stimulus Input

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Theodore P. Zahn, Ph.D.	Research Psychologist	LPP, NIMH
Other:	Thomas N. Robinson, Jr.	Guest Researcher	LPP, NIMH

COOPERATING UNITS *(if any)*

NIH Normal Volunteer Office.

LAB/BRANCH

Laboratory of Psychology and Psychopathology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.50	0.5	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 objectives of this project are to investigate relationships among differences in personality, sensory thresholds, and autonomic nervous system (ANS) activity in normal humans and to study racial differences in ANS activity. Bilateral skin conductance and heart rate have been recorded in two sessions in which constant and variable intensity tones and lights are presented and auditory and two-flash thresholds (TFT) determined by methods which permit signal detection analyses. Several standardized personality tests were also given. These include scales of sensation-seeking, extraversion, neuroticism, psychoticism, field dependence and anxiety. In addition comprehensive measures of lateral dominance have been given as well as a measure of "torque" (clockwise drawing of circles) which has been hypothesized to reflect a neurointegrative deficit and be related to risk for future psychopathology. The procedures allow determination of the effects of stimulus intensity and heteromodal stimulation on ANS activity. A procedure for manipulating ANS arousal experimentally with minimal distracting effects--a change in posture from supine to standing--is being used to assess the effects of arousal on performance and the effects of personality variables on this relationship. This project allows testing of several theoretical models of the relationships of ANS activity, sensory sensitivity, and personality, some of which have implications for the etiology of psychopathology. Tests of the relationships between laterality in skin conductance variables and behavioral laterality will also be done to see if inferences about lateralized brain function can be made from such variables.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

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Z01 MH 00491-10 LPP

PERIOD COVERED

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PI:	Theodore P. Zahn, Ph.D.	Research Psychologist	LPP, NIMH
Other:	Thomas N. Robinson, Jr.	Guest Researcher	LPP, NIMH

COOPERATING UNITS *(if any)*

NIH Normal Volunteer Office.

LAB/BRANCH

Laboratory of Psychology and Psychopathology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.50	0.5	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.)*

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00500-07 LPP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Cognitive and Perceptual Changes in Affective Illness

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Edward K. Silberman, M.D.	Guest Researcher	LPP/NIMH
Others:	Robert Post, M.D.	Chief	BPB/NIMH
	Jean-Phillippe Boulanger	French National Institute for Health & Medical Research	Cannes, France
	Linda Bierer, M.D.	Medical Staff Fellow	BPB/NIMH
	Thomas Uhde	Chief, AAD	BPB/NIMH
	Rex Cowdry, M.D.	Clinical Director	NIMH
	Steven Taube, M.D.	Walter Reed Army Institute of Research	

COOPERATING UNITS *(if any)*

Biological Psychiatry Branch; Walter Reed Army Institute of Research
French National Institute for Health & Medical Research, Cannes, France

LAB/BRANCH

Laboratory of Psychology and Psychopathology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.75	.5	.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.)*

The purpose of this project is to investigate the cognitive and perceptual changes which are present in, and characteristic of major affective illness and its various clinical and biological subtypes. Two separate studies make up the overall investigation: (1) psychomotor and psychosensory symptoms in patients with affective illness, and (2) lateralized hemispheric function in depression.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00500-07 LPP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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PI:	Edward K. Silberman, M.D.	Guest Researcher	LPP/NIMH
Others:	Robert Post, M.D.	Chief	BPB/NIMH
	Jean-Phillippe Boulanger	French National Institute for Health & Medical Research	Cannes, France
	Linda Bierer, M.D.	Medical Staff Fellow	BPB/NIMH
	Thomas Uhde	Chief, AAD	BPB/NIMH
	Rex Cowdry, M.D.	Clinical Director	NIMH
	Steven Taube, M.D.	Walter Reed Army Institute of Research	

COOPERATING UNITS *(if any)*

Biological Psychiatry Branch; Walter Reed Army Institute of Research
French National Institute for Health & Medical Research, Cannes, France

LAB/BRANCH

Laboratory of Psychology and Psychopathology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.75	.5	.25

CHECK APPROPRIATE BOX(ES)

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

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☐ (a2) Interviews

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00503-06 LPP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Human Clinical Studies of Attention Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Allan F. Mirsky Chief LPP, NIMH

COOPERATING UNITS *(if any)*

Epilepsy Branch, NINCDS; Clinical Neurosciences Branch, NINCDS; Laboratory of Clinical Sciences, NIMH; Neuropsychiatry Branch, NIMH; Boston University

LAB/BRANCH

Laboratory of Psychology and Psychopathology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	1.25	.75

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 research comprises three related areas of investigation concerned with specifying neuropsychological factors underlying clinical conditions in humans in which disturbed attention is a major symptom. A major emphasis is on (1) illuminating the nature of brain stem pathophysiology, if any, in such entities as petit mal or absence epilepsy, infantile autism, schizophrenia, and related diseases; (2) an additional major emphasis is on extending the neurobehavioral analysis of attention loss in absence epilepsy so as to facilitate developing alternative treatment strategies for such patients. Both of these projects form part of a larger effort which is aimed at (3) developing a comprehensive and systematic taxonomy of attentional disorders in humans. This latter study will eventually comprise study of patients with cerebral lesions, seizures, dementing diseases, and metabolic illnesses of the brain.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00503-06 LPP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Human Clinical Studies of Attention Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Allan F. Mirsky Chief LPP, NIMH

COOPERATING UNITS *(if any)*

Epilepsy Branch, NINCDS; Clinical Neurosciences Branch, NINCDS; Laboratory of Clinical Sciences, NIMH; Neuropsychiatry Branch, NIMH; Boston University

LAB/BRANCH

Laboratory of Psychology and Psychopathology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	1.25	.75

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.)*

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 00504-06 LPP

PERIOD COVERED: October 1, 1985 to September 30, 1986

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

Models in the Monkey of Generalized Seizures of the Absence Type

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Allan F. Mirsky, Ph.D.	Chief	LPP, NIMH
Others:	Eva Bakay Pragay, Ph.D.	Research Psychologist	LPP, NIMH
	Richard Nakamura, Ph.D.	Guest Researcher	LPP, NIMH
	Michael Myslobodsky, M.D., Ph.D.	Professor, Univ of Tel Aviv	Israel
	Richard Coppola, Ph.D.	Engineer	BPB, NIMH

COOPERATING UNITS *(if any)*

Tel-Aviv University, Israel

LAB/BRANCH

Laboratory of Psychology and Psychopathology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.7	0.7	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.)*

Generalized seizure activity with the electrographic appearance of absence epilepsy (bilaterally symmetrical and synchronous paroxysmal three-per-second spike and wave discharges) can be elicited in the monkey by a variety of methods. These include electrical stimulation of various locations within the brain, injection of convulsant drugs and other substances, and administration of compounds which may alter normal inhibitory mechanisms within the cell. Model seizure states created in these ways are studied in order to test hypotheses about pathophysiological seizure mechanisms, sensory processing and attentional capacities during absence seizures, effects of spike-wave activity on cellular activity, and effects of techniques or maneuvers which may modify or reduce convulsive activity. Most recently this project has involved the following work: we studied the (paradoxical) seizure-inducing effects of a GABA-enhancer and the effects on auditory brain stem evoked potentials of generalized seizures induced by injection of pentylenetetrazol.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00504-06 LPP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Models in the Monkey of Generalized Seizures of the Absence Type

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Allan F. Mirsky, Ph.D.	Chief	LPP, NIMH
Others:	Eva Bakay Pragay, Ph.D.	Research Psychologist	LPP, NIMH
	Richard Nakamura, Ph.D.	Guest Researcher	LPP, NIMH
	Michael Myslobodsky, M.D., Ph.D.	Professor, Univ of Tel Aviv	Israel
	Richard Coppola, Ph.D.	Engineer	BPB, NIMH

COOPERATING UNITS *(if any)*

Tel-Aviv University, Israel

LAB/BRANCH

Laboratory of Psychology and Psychopathology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.7	0.7	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.)*

Generalized seizure activity with the electrographic appearance of absence epilepsy (bilaterally symmetrical and synchronous paroxysmal three-per-second spike and wave discharges) can be elicited in the monkey by a variety of methods. These include electrical stimulation of various locations within the brain, injection of convulsant drugs and other substances, and administration of compounds which may alter normal inhibitory mechanisms within the cell. Model seizure states created in these ways are studied in order to test hypotheses about pathophysiological seizure mechanisms, sensory processing and attentional capacities during absence seizures, effects of spike-wave activity on cellular activity, and effects of techniques or maneuvers which may modify or reduce convulsive activity. Most recently this project has involved the following work: we studied the (paradoxical) seizure-inducing effects of a GABA-enhancer and the effects on auditory brain stem evoked potentials of generalized seizures induced by injection of pentylenetetrazol.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00505-06 LPP

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
State Change Effects on Visual Processing and Attention

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Richard K. Nakamura, Ph.D. Guest Researcher LPP/NIMH

COOPERATING UNITS *(if any)*

Laboratory of Neuropsychology, Laboratory of Cerebral Metabolism, and Neuropsychiatry Branch, NIMH

LAB/BRANCH
Laboratory of Psychology and Psychopathology

SECTION

INSTITUTE AND LOCATION
NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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 in the Monkey Brain: We have been developing a transcortical (surface-to-depth) event-related potential (ERP) method to follow the path of cortical information processing across the monkey brain. The transcortical ERPs will be compared to neural activity in the monkey as well as to ERPs measured from the scalp in both monkeys and humans. Such comparisons will establish the neurophysiological and anatomical basis for the human ERPs that have been shown to be linked to interesting cognitive events.

We map ERP across the brain during information processing of a go/no-go visual discrimination task in the monkey. The ERPs are recorded via transcortical (surface-to-depth) electrodes implanted in sets of up to 37 pairs in each monkey. Space-time images of that activity are then constructed. We have previously reported on the reliability, replicability, sensitivity to task manipulation of the data generated (see 1984 annual report).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00505-06 LPP

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
State Change Effects on Visual Processing and Attention

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Richard K. Nakamura, Ph.D. Guest Researcher LPP/NIMH

COOPERATING UNITS *(if any)*

Laboratory of Neuropsychology, Laboratory of Cerebral Metabolism, and Neuropsychiatry Branch, NIMH

LAB/BRANCH
Laboratory of Psychology and Psychopathology

SECTION

INSTITUTE AND LOCATION
NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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 in the Monkey Brain: We have been developing a transcortical (surface-to-depth) event-related potential (ERP) method to follow the path of cortical information processing across the monkey brain. The transcortical ERPs will be compared to neural activity in the monkey as well as to ERPs measured from the scalp in both monkeys and humans. Such comparisons will establish the neurophysiological and anatomical basis for the human ERPs that have been shown to be linked to interesting cognitive events.

We map ERP across the brain during information processing of a go/no-go visual discrimination task in the monkey. The ERPs are recorded via transcortical (surface-to-depth) electrodes implanted in sets of up to 37 pairs in each monkey. Space-time images of that activity are then constructed. We have previously reported on the reliability, replicability, sensitivity to task manipulation of the data generated (see 1984 annual report).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 00508-04 LPP

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Neuropsychological Evaluation of Psychiatric and Neurological Patients

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Connie C. Duncan, Ph.D. Chief, Unit on Psychophysiology LPP, NIMH

COOPERATING UNITS *(if any)*
Biological Psychiatry Branch, Laboratory of Clinical Science, NIMH; Medical Neurology Branch, Developmental and Metabolic Neurology Branch, NINCDS; Albert Einstein College of Medicine; Chestnut Lodge Hospital; Johns Hopkins University; Maryland Head Injury Foundation.

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Laboratory of Psychology and Psychopathology

SECTION

INSTITUTE AND LOCATION
NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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 comprehensive neuropsychological test battery is used to provide a complete assessment of various cognitive and sensory functions that can be related to damage or dysfunction in different regions of the brain. The battery comprises tests designed to tap the following aspects of behavior: executive functions, language, attention, visual-spatial capacity, memory, and motor behavior. In addition, measures of psychometric intelligence, personality, visual acuity, color vision, and hand and eye dominance are included. The battery provides a thorough assessment of the neurobehavioral capacities of the various categories of patients who are studied by investigators in the LPP. The data thus provide a complete behavioral profile against which to relate the neurophysiological, neuroradiological, and biochemical information that is gathered concurrently on these patients. The data can also provide neurobehaviorally-defined subgroups aimed at reducing variability in psychiatric diagnosis, treatment, and outcome.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00509-04 LPP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Attention Disorders As Assessed by Event-Related Brain Potentials

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Connie C. Duncan, Ph.D., Chief, Unit on Psychophysiology, LPP, NIMH

COOPERATING UNITS *(if any)* Laboratory of Clinical Science, Neuropsychiatry Branch, Child Psychiatry Branch, Clinical Psychobiology Branch, NIMH; Medical Neurology Branch, Developmental Neurology Branch, NINCDS; Laboratory of Neuroscience, NIA; Chestnut Lodge Hospital; University of Pittsburgh; Johns Hopkins University; Maryland Head Injury Foundation.

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Laboratory of Psychology and Psychopathology

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INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.9	1.9	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 aim of this project is to investigate the roles of event-related brain potentials, attention, and information processing and their interrelationships in the etiology, pathology, and prognosis of psychiatric and neurological disorders. Major emphasis is on the diagnostic specificity of disorders of attention and cognition and identification of the specific aspects or stages of information processing underlying observed decrements in performance. Concurrently recorded event-related brain potentials and performance on cognitive tasks are used to define mechanisms of cognitive failure in subjects with diagnoses of schizophrenia, seasonal affective disorder, seizures, attention deficit disorder, learning disorders, eating disorders, and dementing diseases. Event-related brain potentials are also used to investigate the role of altered neurochemical mechanisms by comparing drug-induced electrophysiological and behavioral effects with those seen in the various disorders. Psychological correlates are investigated by relating the data to extensive neuropsychological, psychiatric, and personality measures as well as performance on behavioral tasks.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 00509-04 LPP

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Attention Disorders As Assessed by Event-Related Brain Potentials

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Connie C. Duncan, Ph.D., Chief, Unit on Psychophysiology, LPP, NIMH

COOPERATING UNITS *(if any)* Laboratory of Clinical Science, Neuropsychiatry Branch, Child Psychiatry Branch, Clinical Psychobiology Branch, NIMH; Medical Neurology Branch, Developmental Neurology Branch, NINCDS; Laboratory of Neuroscience, NIA; Chestnut Lodge Hospital; University of Pittsburgh; Johns Hopkins University; Maryland Head Injury Foundation.

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Laboratory of Psychology and Psychopathology

SECTION

INSTITUTE AND LOCATION
NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.9	1.9	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 aim of this project is to investigate the roles of event-related brain potentials, attention, and information processing and their interrelationships in the etiology, pathology, and prognosis of psychiatric and neurological disorders. Major emphasis is on the diagnostic specificity of disorders of attention and cognition and identification of the specific aspects or stages of information processing underlying observed decrements in performance. Concurrently recorded event-related brain potentials and performance on cognitive tasks are used to define mechanisms of cognitive failure in subjects with diagnoses of schizophrenia, seasonal affective disorder, seizures, attention deficit disorder, learning disorders, eating disorders, and dementing diseases. Event-related brain potentials are also used to investigate the role of altered neurochemical mechanisms by comparing drug-induced electrophysiological and behavioral effects with those seen in the various disorders. Psychological correlates are investigated by relating the data to extensive neuropsychological, psychiatric, and personality measures as well as performance on behavioral tasks.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02235-02 LPP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Topographic Analysis of Brain Activity

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: Richard Coppola, D.Sc. Senior Engineer LPP/NIMH

COOPERATING UNITS *(if any)* Laboratory of Cerebral Metabolism, Neuroscience Branch, Biological Psychiatry Branch, Neuropsychiatry Branch, Laboratory of Clinical Sciences, and Child Psychiatry Branch, NIMH; Epilepsy Branch, NINCDS; Laboratory of Clinical Studies, NIAAA; Laboratory of Neuroscience, NIA

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Laboratory of Psychology and Psychopathology

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INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

Electrical brain activity, as an index of central nervous system function, is studied across a range of patient groups with neurological and psychiatric disorders as well as normal volunteers. Using electrophysiological data quantified from event-related potentials and spectrum analysis of EEG recordings, computer-derived brain images are able to provide information about neurophysiological function relating to both cognition and clinical state. Topographic maps efficiently characterize spatial and temporal patterns of brain activity allowing the ability to study the dynamic interaction among brain regions and their relation to function.

The project has two main purposes. The first is to refine the topographic and quantitative analysis methods and establish normative data for various conditions and activation procedures. For example, normal subjects differ with respect to their major focus of resting EEG alpha rhythm; one group shows a dominant parietal locus and one an occipital locus, depending on the alpha frequency.

The second purpose is to apply these methods to the characterization of clinical groups and pharmacological response. Work in progress includes characterization of subgroups of Alzheimer's patients, localization of abnormality in epilepsy patients, localization of drug activation and study of psychiatric patients on various neuroleptic drugs.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02288-02 LPP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Studies on Etiological Factors in Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Seymour S. Kety, M.D.	Senior Scientist, NIMH
Others:	Paul Wender, M.D.	Prof Psychiatry, Univ. of Utah
	Bjorn Jacobsen, M.D.	Assoc Prof Psychiatry, Univ. of Copenhagen
	Fini Schulsinger, M.D.	Prof. Psychiatry, Univ of Copenhagen
	Dennis Kinney, Ph.D.	Asst Prof Psychiatry, Harvard University
	Loring Ingraham, Ph.D.	Staff Fellow, LPP, NIMH

COOPERATING UNITS *(if any)*

Psychological Institute, Copenhagen, Denmark; McLean Hospital, Belmont, Mass.; Harvard University; University of Utah; Medical College of Virginia.

LAB/BRANCH

Laboratory of Psychology and Psychopathology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

Studies of the occurrence of mental illness in families have been useful in identifying familial forms of the illnesses and in the development of hypotheses regarding the form and strength of genetic and environmental factors in etiology. Where these major variables are separated by the process of adoption, specific etiologic hypotheses can be tested separately and in combination. A total national sample of 14,500 adult adoptees in Denmark provides the basis of this research. One major study has focused on 42 schizophrenic adoptees, the other on 71 adoptees with manic-depressive or other affective disorder identified in the national sample with a comparable number of matched control adoptees never hospitalized for mental illness. The remarkable population registers in Denmark permit the identification of the close biological and adoptive relatives of these adoptees. By search of mental hospital registers and ultimately by personal interviews, information on the psychiatric history and status of the relatives has been obtained.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02288-02 LPP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Studies on Etiological Factors in Schizophrenia

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PI:	Seymour S. Kety, M.D.	Senior Scientist, NIMH
Others:	Paul Wender, M.D.	Prof Psychiatry, Univ. of Utah
	Bjorn Jacobsen, M.D.	Assoc Prof Psychiatry, Univ. of Copenhagen
	Fini Schulsinger, M.D.	Prof. Psychiatry, Univ of Copenhagen
	Dennis Kinney, Ph.D.	Asst Prof Psychiatry, Harvard University
	Loring Ingraham, Ph.D.	Staff Fellow, LPP, NIMH

COOPERATING UNITS *(if any)*

Psychological Institute, Copenhagen, Denmark; McLean Hospital, Belmont, Mass.; Harvard University; University of Utah; Medical College of Virginia.

LAB/BRANCH

Laboratory of Psychology and Psychopathology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02295-01 LPP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Genetic Factors in Response to Alcohol

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Connie C. Duncan, Ph.D.	Senior Staff Fellow	LPP/NIMH
Co-PI:	Frances H. Gabbay, Ph.D.	Guest Researcher	LPP/NIMH
Others:	Allan F. Mirsky, Ph.D.	Chief	LPP/NIMH
	T. Peter Bridge, M.D.	Science Advisor	OA/ADAMHA

COOPERATING UNITS *(if any)*

Department of Mental Hygiene, School of Hygiene and Public Health, Johns Hopkins University

LAB/BRANCH

Laboratory of Psychology and Psychopathology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.1	0.9	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 assess the relative contributions of genetic and environmental factors to alcohol drinking and response to alcohol challenge. The project is composed of two studies. In the first, 100 male monozygotic (MZ) and 100 male dizygotic (DZ) twin pairs will complete a questionnaire describing their alcohol and other drug use and a 28-day record of their alcohol intake. These data will permit estimation of the relative contributions of genetic and environmental factors to frequency and amount of alcohol consumption. In addition, comparison of questionnaire estimates of alcohol intake with those obtained by the 28-day record will allow assessment of the validity of the questionnaire method. In the second study, 15 male MZ and 15 male DZ twin pairs will receive a placebo and two doses of alcohol (0.40 g/kg and 0.80 g/kg). The protocol will consist of electrophysiological measures (e.g., brainstem auditory evoked responses, resting EEG, and visual and auditory event-related brain potentials), self-reports of affect, and a measure of standing stability. The use of placebo and multiple doses will permit conclusions about the effects of alcohol on information processing, mood, and motor activity. The twin design will provide information on the relative contributions of genetic and environmental factors to variability in these measures in the drug-free state and following response to alcohol challenge. Finally, conclusions regarding the stability of these measures within individuals across time will be based on comparisons of baseline measures across the three sessions.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02295-01 LPP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Genetic Factors in Response to Alcohol

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Connie C. Duncan, Ph.D.	Senior Staff Fellow	LPP/NIMH
Co-PI:	Frances H. Gabbay, Ph.D.	Guest Researcher	LPP/NIMH
Others:	Allan F. Mirsky, Ph.D.	Chief	LPP/NIMH
	T. Peter Bridge, M.D.	Science Advisor	OA/ADAMHA

COOPERATING UNITS *(if any)*

Department of Mental Hygiene, School of Hygiene and Public Health, Johns Hopkins University

LAB/BRANCH

Laboratory of Psychology and Psychopathology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.1	0.9	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 assess the relative contributions of genetic and environmental factors to alcohol drinking and response to alcohol challenge. The project is composed of two studies. In the first, 100 male monozygotic (MZ) and 100 male dizygotic (DZ) twin pairs will complete a questionnaire describing their alcohol and other drug use and a 28-day record of their alcohol intake. These data will permit estimation of the relative contributions of genetic and environmental factors to frequency and amount of alcohol consumption. In addition, comparison of questionnaire estimates of alcohol intake with those obtained by the 28-day record will allow assessment of the validity of the questionnaire method. In the second study, 15 male MZ and 15 male DZ twin pairs will receive a placebo and two doses of alcohol (0.40 g/kg and 0.80 g/kg). The protocol will consist of electrophysiological measures (e.g., brainstem auditory evoked responses, resting EEG, and visual and auditory event-related brain potentials), self-reports of affect, and a measure of standing stability. The use of placebo and multiple doses will permit conclusions about the effects of alcohol on information processing, mood, and motor activity. The twin design will provide information on the relative contributions of genetic and environmental factors to variability in these measures in the drug-free state and following response to alcohol challenge. Finally, conclusions regarding the stability of these measures within individuals across time will be based on comparisons of baseline measures across the three sessions.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 00478-30 LN

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Neural mechanisms of cognitive memory and habit formation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	M. Mishkin	Chief	LN NIMH
Others:	E.A. Murray	Senior Staff Fellow	LN NIMH
	J. Bachevalier	Visiting Scientist	LN NIMH
	R.C. Saunders	Staff Fellow	LN NIMH
	H. Petri	Chairman	Towson State Univ.
	W. Overman	Asst. Professor	Univ. of North Carolina
	S. Suomi	Chief	LCE NICHD
	D. Olton	Professor	Johns Hopkins Univ.

COOPERATING UNITS *(if any)*
Towson State University
University of North Carolina
National Institute of Child Health and Human Development
Johns Hopkins University

LAB/BRANCH
Laboratory of Neuropsychology

SECTION

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
6.0	2.5	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.)*

Every sensory modality in the macaque is served by a series of cortical stations, each of which processes the sensory signal in turn. Signals in the later stations, located in the anterior temporo-insular cortex, can activate a circuit that runs through the limbic system to the neuromodulatory systems (e.g. cholinergic, noradrenergic, etc.) and back to the sensory cortical stations. We have proposed that as a result of the action of this circuit on neuromodulator release in sensory cortex, some of the neurons whose signals have just represented the sensory stimulus become linked together in a cell assembly that serves as the stored representation of that stimulus. Recognition, say of an object, occurs when an assembly formed on a first presentation of the object is reactivated by its re-presentation on a second occasion. Also, once formed, that assembly can be linked to assemblies representing other stimuli and other events, such as a food reward or a location, thereby investing the recognized object with meaning. The linkage involved in object-reward association appears to be mediated mainly by a limbo-neuromodulatory circuit running through the amygdala, the medial dorsal thalamic nucleus, orbital frontal cortex, and the basal nucleus of Meynert. Similarly, the linkage involved in object-place association seems to be mediated mainly by a second, parallel limbo-neuromodulatory circuit running through the hippocampus, the anterior thalamic nuclei, cingulate cortex, and the medial septal and diagonal band nuclei. Each of these circuits has reciprocal connections with one pair or the other of the assemblies described above. Thus, if these circuits have been activated, the sight of the object on a second occasion can lead not only to its recognition but also to recall of the food reward and the spatial location with which the object had been associated. Recognition and recall are two forms of cognitive memory, both of which can be distinguished from habit formation. The latter form of learning involves stimulus-response association specifically, and we have proposed that such learning depends largely on interactions between the cerebral cortex and the basal ganglia.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 00478-30 LN

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Neural mechanisms of cognitive memory and habit formation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	M. Mishkin	Chief	LN NIMH
Others:	E.A. Murray	Senior Staff Fellow	LN NIMH
	J. Bachevalier	Visiting Scientist	LN NIMH
	R.C. Saunders	Staff Fellow	LN NIMH
	H. Petri	Chairman	Towson State Univ.
	W. Overman	Asst. Professor	Univ. of North Carolina
	S. Suomi	Chief	LCE NICHD
	D. Olton	Professor	Johns Hopkins Univ.

COOPERATING UNITS *(if any)*
Towson State University
University of North Carolina
National Institute of Child Health and Human Development
Johns Hopkins University

LAB/BRANCH
Laboratory of Neuropsychology

SECTION

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
6.0	2.5	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.)*

Every sensory modality in the macaque is served by a series of cortical stations, each of which processes the sensory signal in turn. Signals in the later stations, located in the anterior temporo-insular cortex, can activate a circuit that runs through the limbic system to the neuromodulatory systems (e.g. cholinergic, noradrenergic, etc.) and back to the sensory cortical stations. We have proposed that as a result of the action of this circuit on neuromodulator release in sensory cortex, some of the neurons whose signals have just represented the sensory stimulus become linked together in a cell assembly that serves as the stored representation of that stimulus. Recognition, say of an object, occurs when an assembly formed on a first presentation of the object is reactivated by its re-presentation on a second occasion. Also, once formed, that assembly can be linked to assemblies representing other stimuli and other events, such as a food reward or a location, thereby investing the recognized object with meaning. The linkage involved in object-reward association appears to be mediated mainly by a limbo-neuromodulatory circuit running through the amygdala, the medial dorsal thalamic nucleus, orbital frontal cortex, and the basal nucleus of Meynert. Similarly, the linkage involved in object-place association seems to be mediated mainly by a second, parallel limbo-neuromodulatory circuit running through the hippocampus, the anterior thalamic nuclei, cingulate cortex, and the medial septal and diagonal band nuclei. Each of these circuits has reciprocal connections with one pair or the other of the assemblies described above. Thus, if these circuits have been activated, the sight of the object on a second occasion can lead not only to its recognition but also to recall of the food reward and the spatial location with which the object had been associated. Recognition and recall are two forms of cognitive memory, both of which can be distinguished from habit formation. The latter form of learning involves stimulus-response association specifically, and we have proposed that such learning depends largely on interactions between the cerebral cortex and the basal ganglia.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02032-10 LN

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Neural coding of visual stimuli in the awake monkey

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	B.J. Richmond	Senior Surgeon	LN NIMH
Others:	L. Optican	Senior Staff Fellow	LSR NEI
	H. Spitzer	Visiting Fellow	LN NIMH
	M. Mishkin	Chief	LN NIMH

COOPERATING UNITS *(if any)*

Laboratory of Sensorimotor Research, NEI

LAB/BRANCH

Laboratory of Neuropsychology

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	1.5	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.)*

Single neurons were recorded from both the first and last cortical stations of the visual system of monkeys to study mechanisms underlying visual perception and memory. Neurons in both these regions, striate cortex and inferior temporal cortex, showed different temporal sequences of action potentials in response to different visual stimulus patterns. Analysis of the responses of these neurons as if they were information carriers in communications channels revealed that different temporal patterns of neuronal activity conveyed different information about stimulus features. In both these cortical regions, several (3-6) simultaneous, independent temporal patterns were needed to represent the modulation of the stimulus driven neuronal activity. A code made up of three simultaneous temporal patterns conveyed twice as much information about the stimulus as a more traditional measure of the response, the number of action potentials. This suggests a new hypothesis about visual processing, the multiplex-filter hypothesis: visual system neurons act as if they transmit several simultaneous or multiplexed messages describing the stimulus. In a test of this hypothesis, the responses of complex cells from striate cortex were characterized using a small set (16) of one-dimensional basic stimuli. A computer simulation of neuronal responsiveness based on the multiplex-filter hypothesis successfully predicted the actual temporally modulated responses of these neurons to 44 other one-dimensional patterns.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

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	H. Spitzer	Visiting Fellow	LN NIMH
	M. Mishkin	Chief	LN NIMH

COOPERATING UNITS *(if any)*

Laboratory of Sensorimotor Research, NEI

LAB/BRANCH

Laboratory of Neuropsychology

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	1.5	1.0

CHECK APPROPRIATE BOX(ES)

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☐ (a1) Minors

☐ (a2) Interviews

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

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02033-09 LN

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Functional mapping of sensory and memory systems

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	R.C. Saunders	Staff Fellow	LN NIMH
Others:	M. Mishkin	Chief	LN NIMH
	K.A. Macko	Guest Researcher	LN NIMH
	J. Bachevalier	Visiting Scientist	LN NIMH
	C. Kennedy	Guest Researcher	LCM NIMH
	L. Sokoloff	Chief	LCM NIMH
	R.K. Nakamura	Chief	NR-B NIDA

COOPERATING UNITS *(if any)*

Laboratory of Cerebral Metabolism, NIMH
National Institute on Drug Abuse

LAB/BRANCH

Laboratory of Neuropsychology

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	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 cerebral areas related to vision in the rhesus monkey were identified by comparison of metabolic activity in visually stimulated versus visually deafferented cerebral hemispheres. The results allowed delineation of the visual-nonvisual borders of both an occipitotemporal and an occipitoparietal visual pathway and specification of their points of interaction with frontal, limbic, striatal, and diencephalic structures. In addition, it was found that, within the occipitotemporal pathway, the forebrain commissures contribute to the visual activation of area TE only. Finally, the functional development of the visual system as reflected in its metabolic activity was traced in a series of infant monkeys and was found to reach adult levels at about 4 months postnatally.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

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Z01 MH 02033-09 LN

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COOPERATING UNITS *(if any)*

Laboratory of Cerebral Metabolism, NIMH
National Institute on Drug Abuse

LAB/BRANCH

Laboratory of Neuropsychology

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	0.0

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☐ (a1) Minors

☐ (a2) Interviews

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

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02035-06 LN

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Anatomy of the primate visual system

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	L.G. Ungerleider	Research Psychologist	LN NIMH
Others:	M. Mishkin	Chief	LN NIMH
	R. Desimone	Senior Staff Fellow	LN NIMH
	J. Saint-Cyr	Guest Researcher	LN NIMH
	R.J. Tusa	Asst. Professor	Johns Hopkins Univ.

COOPERATING UNITS *(if any)*

Johns Hopkins University

LAB/BRANCH

Laboratory of Neuropsychology

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.0	1.0	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.)*

To better understand the role of visual association cortex in perception and memory, we have been examining the multiple functional areas that comprise this cortex in the macaque and exploring their interconnections by the use of neuroanatomical tracing techniques in combination with electrophysiological recording. Our results indicate that the primary visual area (V1), or striate cortex, is the source of two divergent corticocortical pathways: one, an occipitotemporal pathway, which enables the visual recognition of objects; the other, an occipitoparietal pathway, which mediates the appreciation of the spatial relationships among objects. The visual areas along the occipitotemporal pathway (V1, V2, V3, V4, and areas TEO and TE of the inferior temporal cortex) appear to be organized primarily as a serial hierarchy, in which each area processes several different stimulus attributes in parallel. This pathway is modality-specific throughout its extent, unlike the occipitoparietal pathway, in which the later stations are polysensory. Whereas area V4 provides a major link forward from striate cortex into the temporal lobe, our results on visual area MT indicate that it provides a major link forward from striate cortex into the parietal lobe via its projections to three separate areas in the superior temporal and intraparietal sulci. However, MT does not provide the sole route by which visual information from striate cortex reaches the parietal lobe. Other potential pathways are provided by several additional visual areas located in occipito-parietal cortex. Most of these areas receive inputs representing predominantly the peripheral visual field, which presumably reflects the importance of such inputs for spatial vision. By contrast, the predominance of central visual field inputs to V4 and TEO in the temporal lobe presumably reflects the importance of these inputs for object vision.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02035-06 LN

PERIOD COVERED

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PI:	L.G. Ungerleider	Research Psychologist	LN NIMH
Others:	M. Mishkin	Chief	LN NIMH
	R. Desimone	Senior Staff Fellow	LN NIMH
	J. Saint-Cyr	Guest Researcher	LN NIMH
	R.J. Tusa	Asst. Professor	Johns Hopkins Univ.

COOPERATING UNITS *(if any)*

Johns Hopkins University

LAB/BRANCH

Laboratory of Neuropsychology

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.0	1.0	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.)*

To better understand the role of visual association cortex in perception and memory, we have been examining the multiple functional areas that comprise this cortex in the macaque and exploring their interconnections by the use of neuroanatomical tracing techniques in combination with electrophysiological recording. Our results indicate that the primary visual area (V1), or striate cortex, is the source of two divergent corticocortical pathways: one, an occipitotemporal pathway, which enables the visual recognition of objects; the other, an occipitoparietal pathway, which mediates the appreciation of the spatial relationships among objects. The visual areas along the occipitotemporal pathway (V1, V2, V3, V4, and areas TEO and TE of the inferior temporal cortex) appear to be organized primarily as a serial hierarchy, in which each area processes several different stimulus attributes in parallel. This pathway is modality-specific throughout its extent, unlike the occipitoparietal pathway, in which the later stations are polysensory. Whereas area V4 provides a major link forward from striate cortex into the temporal lobe, our results on visual area MT indicate that it provides a major link forward from striate cortex into the parietal lobe via its projections to three separate areas in the superior temporal and intraparietal sulci. However, MT does not provide the sole route by which visual information from striate cortex reaches the parietal lobe. Other potential pathways are provided by several additional visual areas located in occipito-parietal cortex. Most of these areas receive inputs representing predominantly the peripheral visual field, which presumably reflects the importance of such inputs for spatial vision. By contrast, the predominance of central visual field inputs to V4 and TEO in the temporal lobe presumably reflects the importance of these inputs for object vision.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02036-06 LN

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Neural representations of visual stimuli in the extrastriate cortex

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	R. Desimone	Senior Staff Fellow	LN NIMH
Others:	M. Mishkin	Chief	LN NIMH
	H. Spitzer	Visiting Fellow	LN NIMH
	S.J. Schein	Asst. Prof. of Ophthalmology	Harvard Med. School

COOPERATING UNITS *(if any)*

Harvard Medical School

LAB/BRANCH

Laboratory of Neuropsychology

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	1.5	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 neural mechanisms for the visual recognition of objects extend beyond the primary visual cortex into multiple extrastriate cortical areas within the occipital and temporal lobes. To understand the neural mechanisms of perception, attention and memory in these areas, we are recording the activity of neurons both in anesthetized, immobilized monkeys and in awake monkeys engaged in a task requiring visual discrimination, selective attention, and memory. We have found that neurons in one extrastriate area, area V4, code many different stimulus features useful for object recognition, such as the length and width of contours, textures, and colors. Since neurons in this area are sensitive to form and color differences between a stimulus and its background, they may play a role in separating figure from ground. In both V4 and the inferior temporal cortex, we have found that selective attention gates visual processing by filtering unwanted information from the receptive fields. Even the degree to which attended stimuli are processed in these areas depends on "how much" attention, or effort, is devoted to them. Thus, the information-processing capacity of cortical neurons depends not only on hard-wired mechanisms but on cognitive state. Since we do not find neuronal effects of spatially directed attention in either the primary visual cortex or area V2, whatever structures gate extrastriate responses to attended stimuli must work at the level of V4 and beyond. We are currently attempting to identify these structures.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02037-05 LN

PERIOD COVERED: October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Functional anatomy of the somatosensory cortex of the monkey

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	T.P. Pons	Guest Researcher	LN NIMH
Others:	M. Mishkin	Chief	LN NIMH
	D.P. Friedman	Project Officer	NRB NIDA
	E.A. Murray	Senior Staff Fellow	LN NIMH
	R.J. Schneider	Guest Researcher	LN NIMH
	P.E. Garraghty	Postdoctoral Fellow	Massachusetts Inst. Tech.

COOPERATING UNITS *(if any)*

National Institute on Drug Abuse
Massachusetts Institute of Technology

LAB/BRANCH: Laboratory of Neuropsychology

SECTION:

INSTITUTE AND LOCATION: NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.0	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.)*

To identify a route by which tactile information could reach limbic structures in the temporal lobe, we used axonal transport techniques to trace the connections between somatosensory cortical fields. On the basis of the laminar patterns of these corticocortical connections, we identified them as 'forward' or 'backward' by analogy to similar designations in the visual system, where they have been shown to have functional validity. The analysis indicated that a forward-projecting route could be traced from the subdivisions of the primary somatosensory cortex to the second somatosensory area, SII; from SII to the granular and dysgranular fields of the insula; and from the insula directly to the amygdala and indirectly to the hippocampus via rhinal cortex. This multisynaptic cortico-limbic pathway in the somatosensory system is thus organized in a manner analogous to the multisynaptic cortico-limbic pathway in the visual system. To assess the functional importance of the pathway, we studied the somatosensory receptive fields of neurons in SII cortex following selective ablations within the primary somatosensory cortex and found that elimination of any given representation of the body surface in the postcentral strip eliminated it also in SII. For example, removing the hand representation from the postcentral strip resulted in its disappearance from SII cortex; conversely, removing all other body representations from the postcentral strip (i.e. except that of the hand) resulted in the preservation in SII of the hand representation only. The electrophysiological data thus provide strong support for the conclusion, based originally on the anatomical data, that tactile information is processed sequentially along a corticocortical pathway. The electrophysiological experiments also revealed a surprising degree of functional reorganization in SII cortex following the postcentral cortical ablations. After each partial removal, the vacated representation in SII was filled in by the expansion of the intact, neighboring representations. The findings point to a previously unrecognized degree of cortical plasticity in adult primates following brain injury.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02037-05 LN

PERIOD COVERED
October 1, 1985 to September 30, 1986

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PI:	T.P. Pons	Guest Researcher	LN NIMH
Others:	M. Mishkin	Chief	LN NIMH
	D.P. Friedman	Project Officer	NRB NIDA
	E.A. Murray	Senior Staff Fellow	LN NIMH
	R.J. Schneider	Guest Researcher	LN NIMH
	P.E. Garraghty	Postdoctoral Fellow	Massachusetts Inst. Tech.

COOPERATING UNITS *(if any)*

National Institute on Drug Abuse
Massachusetts Institute of Technology

LAB/BRANCH
Laboratory of Neuropsychology

SECTION

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.0	0.5

CHECK APPROPRIATE BOX(ES)

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☐ (a1) Minors
☐ (a2) Interviews

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

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02038-04 LN

PERIOD COVERED: October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Ontogenetic development of cognitive memory and habit formation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.)* *(Name, title, laboratory, and institute affiliation)*

PI:	J. Bachevalier	Visiting Associate	LN NIMH
Others:	M. Mishkin	Chief	LN NIMH
	P.M. Merjanian	Guest Researcher	LN NIMH
	L.G. Ungerleider	Research Psychologist	LN NIMH
	D.P. Friedman	Guest Researcher	LN NIMH

COOPERATING UNITS *(if any)*: None

LAB/BRANCH: Laboratory of Neuropsychology

SECTION:

INSTITUTE AND LOCATION: NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

Cognitive Memory formation and habit formation are two qualitatively different retention processes based on separate neural mechanisms. On the evidence that the limbic memory system is not fully developed in infant monkeys, we have prepared monkeys with neonatal removal of this system to see how emotional and social behavior develops in animals whose infantile global amnesia might persist through adulthood. Animals with neonatal removal of area TE, a higher-order station of the visual system, serve as controls. The results so far indicate that, at three months of age, neonatal ablation of area TE leads to a transient impairment of habit formation (compared to permanent impairment seen with the same lesion in adults), whereas limbic lesions in both infants and adults leave habit formation intact. Interestingly, data on both normal and operated infants suggest that development of the habit system is sexually dimorphic, and that this is due to the high testosterone levels present in male infants before and shortly after birth. At ten months of age, the infants with limbic lesions show impairment in memory formation, whereas the operated controls show significant functional sparing (compared to those that received the same lesions as adults). These findings point to greater compensatory potential after neonatal cortical than after neonatal limbic removals, indicating that association areas of the cortex are less mature at birth, and may thus possess greater plasticity than limbic structures. Direct evidence of neocortical immaturity in the macaque has been provided by our neurobiological studies on opiate and cholinergic receptor distribution and on metabolic activity. Finally, early dysfunction of the limbo-thalamic memory system produces symptoms that are similar to the behavioral syndrome seen in autistic children, providing an animal model of infantile autism.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02038-04 LN

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Ontogenetic development of cognitive memory and habit formation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J. Bachevalier	Visiting Associate	LN NIMH
Others:	M. Mishkin	Chief	LN NIMH
	P.M. Merjanian	Guest Researcher	LN NIMH
	L.G. Ungerleider	Research Psychologist	LN NIMH
	D.P. Friedman	Guest Researcher	LN NIMH

COOPERATING UNITS *(if any)*
None

LAB/BRANCH
Laboratory of Neuropsychology

SECTION

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

Cognitive Memory formation and habit formation are two qualitatively different retention processes based on separate neural mechanisms. On the evidence that the limbic memory system is not fully developed in infant monkeys, we have prepared monkeys with neonatal removal of this system to see how emotional and social behavior develops in animals whose infantile global amnesia might persist through adulthood. Animals with neonatal removal of area TE, a higher-order station of the visual system, serve as controls. The results so far indicate that, at three months of age, neonatal ablation of area TE leads to a transient impairment of habit formation (compared to permanent impairment seen with the same lesion in adults), whereas limbic lesions in both infants and adults leave habit formation intact. Interestingly, data on both normal and operated infants suggest that development of the habit system is sexually dimorphic, and that this is due to the high testosterone levels present in male infants before and shortly after birth. At ten months of age, the infants with limbic lesions show impairment in memory formation, whereas the operated controls show significant functional sparing (compared to those that received the same lesions as adults). These findings point to greater compensatory potential after neonatal cortical than after neonatal limbic removals, indicating that association areas of the cortex are less mature at birth, and may thus possess greater plasticity than limbic structures. Direct evidence of neocortical immaturity in the macaque has been provided by our neurobiological studies on opiate and cholinergic receptor distribution and on metabolic activity. Finally, early dysfunction of the limbo-thalamic memory system produces symptoms that are similar to the behavioral syndrome seen in autistic children, providing an animal model of infantile autism.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02039-04 LN

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Pharmacology of cognitive memory and habit formation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	T.G. Aigner	Senior Staff Fellow	LN NIMH
Others:	M. Mishkin	Chief	LN NIMH
	R.Q. Wan	Visiting Fellow	LN NIMH
	R.M. Brown	Chief	NS NIDA
	M.R. DeLong	Professor	Johns Hopkins Univ.
	D. Price	Professor	Johns Hopkins Univ.

COOPERATING UNITS *(if any)*

The Johns Hopkins University School of Medicine, Baltimore, MD
National Institute on Drug Abuse

LAB/BRANCH

Laboratory of Neuropsychology

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	1.5	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.)*

Evidence from patients with Alzheimer's disease suggest that the basal forebrain cholinergic system plays an important role in memory functioning. Our results from studies in normal monkeys show that compounds that interfere with cholinergic mechanisms, such as the cholinergic receptor blocker scopolamine, produce impairments in recognition memory. In addition, our results suggest that the effects of scopolamine are mainly anterograde, implying an action on storage rather than retrieval. In a separate study on habit formation, we administered the dopaminergic neurotoxin MPTP. This compound failed to impair learning at doses that did not disrupt motor function. Based on previous results suggesting that THC may be exerting its effects through an action on the limbic system, we administered this drug to monkeys performing spatial reversal, a task known to be sensitive to hippocampal damage. Doses of THC that impaired recognition memory did not affect performance on this task.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02039-04 LN

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(60 characters or less. Title must fit on one line between the borders.)*
Pharmacology of cognitive memory and habit formation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	T.G. Aigner	Senior Staff Fellow	LN NIMH
Others:	M. Mishkin	Chief	LN NIMH
	R.Q. Wan	Visiting Fellow	LN NIMH
	R.M. Brown	Chief	NS NIDA
	M.R. DeLong	Professor	Johns Hopkins Univ.
	D. Price	Professor	Johns Hopkins Univ.

COOPERATING UNITS *(if any)*
The Johns Hopkins University School of Medicine, Baltimore, MD
National Institute on Drug Abuse

LAB/BRANCH
Laboratory of Neuropsychology

SECTION

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	1.5	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.)*

Evidence from patients with Alzheimer's disease suggest that the basal forebrain cholinergic system plays an important role in memory functioning. Our results from studies in normal monkeys show that compounds that interfere with cholinergic mechanisms, such as the cholinergic receptor blocker scopolamine, produce impairments in recognition memory. In addition, our results suggest that the effects of scopolamine are mainly anterograde, implying an action on storage rather than retrieval. In a separate study on habit formation, we administered the dopaminergic neurotoxin MPTP. This compound failed to impair learning at doses that did not disrupt motor function. Based on previous results suggesting that THC may be exerting its effects through an action on the limbic system, we administered this drug to monkeys performing spatial reversal, a task known to be sensitive to hippocampal damage. Doses of THC that impaired recognition memory did not affect performance on this task.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02040-03 LN

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Functional analysis of neurotransmitter systems

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	T.P. Pons	Guest Researcher	LN NIMH
Others:	M. Mishkin	Chief	LN NIMH
	D.P. Friedman	Guest Researcher	LN NIMH
	J. Bachevalier	Visiting Scientist	LN NIMH
	L.G. Ungerleider	Research Psychologist	LN NIMH
	C.B. Pert	Chief, Sec. Brain Chemistry	NSB NIMH
	A. Routtenberg	Professor	Northwestern Univ.

COOPERATING UNITS *(if any)*

Section on Brain Chemistry, NIMH
Northwestern University

LAB/BRANCH

Laboratory of Neuropsychology

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.0	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.)*

Many neuromodulatory systems of the brain have been implicated in higher order functions, both cognitive and emotional. To help identify their specific sites and modes of action, we have undertaken studies in macaques to localize several neuromodulator receptors of interest and to determine some of their functional properties. The levels of mu opiate receptors in different cortical sensory areas was found to be linked to the rates of protein phosphorylation in the F1 band in these same areas; since phosphorylation of the F1 protein has been correlated with learning and memory, the results suggest that opiates may exert local control over the learning-related phosphorylation process. Cerebral localization of benzodiazepine and beta-carboline receptors indicate that the two receptor types are distributed nearly identically, implying that both drugs act on the same brain regions to produce their effects on anxiety. The cortical laminar distribution of nicotinic and muscarinic cholinergic binding sites suggests that nicotinic receptors probably modulate sensory processing, whereas muscarinic receptors are more likely to be involved in sensory information storage.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02040-03 LN

PERIOD COVERED
October 1, 1985 to September 30, 1986

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

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	T.P. Pons	Guest Researcher	LN NIMH
Others:	M. Mishkin	Chief	LN NIMH
	D.P. Friedman	Guest Researcher	LN NIMH
	J. Bachevalier	Visiting Scientist	LN NIMH
	L.G. Ungerleider	Research Psychologist	LN NIMH
	C.B. Pert	Chief, Sec. Brain Chemistry	NSB NIMH
	A. Routtenberg	Professor	Northwestern Univ.

COOPERATING UNITS *(if any)*

Section on Brain Chemistry, NIMH
Northwestern University

LAB/BRANCH
Laboratory of Neuropsychology

SECTION

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.0	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.)*

Many neuromodulatory systems of the brain have been implicated in higher order functions, both cognitive and emotional. To help identify their specific sites and modes of action, we have undertaken studies in macaques to localize several neuromodulator receptors of interest and to determine some of their functional properties. The levels of mu opiate receptors in different cortical sensory areas was found to be linked to the rates of protein phosphorylation in the F1 band in these same areas; since phosphorylation of the F1 protein has been correlated with learning and memory, the results suggest that opiates may exert local control over the learning-related phosphorylation process. Cerebral localization of benzodiazepine and beta-carboline receptors indicate that the two receptor types are distributed nearly identically, implying that both drugs act on the same brain regions to produce their effects on anxiety. The cortical laminar distribution of nicotinic and muscarinic cholinergic binding sites suggests that nicotinic receptors probably modulate sensory processing, whereas muscarinic receptors are more likely to be involved in sensory information storage.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00680-04 LSES

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Work Experiences and the Deinstitutionalized Mentally Ill

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Elliot Liebow, Guest Researcher, LSES, NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Socio-environmental Studies

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

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 exploratory, participant observation study is to examine the work experience of the deinstitutionalized mentally ill over time and to seek out ways in which job characteristics, symptoms, and social relationships interact with one another to effect the course of recovery from psychiatric disorder and reintegration into the community. Field work was carried out with residents of halfway houses, participants in community-based psychosocial and transitional work programs, and with "unattached" deinstitutionalized men and women.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00679-06 LSES

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Structural Equation Models in the Analysis of Data with Measurement Error

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Ronald J. Schoenberg, Research Sociologist	LSES	NIMH
OTHER:	C. Schooler, Acting Chief	LSES	NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Socio-environmental Studies

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.60	1.10	.50

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 work is to further develop the methods and techniques for the specification and estimation of the parameters of structural equation models of survey data that contain random and nonrandom measurement error. Included in this are methods for the identification of the models, estimation of the means of unobserved variables, the determination of model condition, and the treatment of polytomous variables.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00672-21 LSES

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Social Psychological Correlates of Occupational Position

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: C. Schooler, Acting Chief, Laboratory of Socio-environmental Studies, NIMH

OTHER:	C. Schoenbach	Social Science Analyst	LSES	NIMH
	M. Kohn	Guest Researcher	LSES	NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Socio-environmental Studies

SECTION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

INSTITUTE AND LOCATION

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.90	1.90	4.00

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 object of this study is to assess the reciprocal effects of occupational conditions and psychological functioning (in particular, values, self-conceptions, social orientation, and intellectual flexibility). Structured interviews were conducted in 1964 with a sample of 3101 men, representative of all men employed in civilian occupations throughout the United States. The study was extended into a longitudinal study in 1974, with the reinterviewing of a randomly-selected one-fourth of the original sample, together with their wives and, where appropriate, one of their children. Replications of this research have been carried out in Poland and Japan.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00672-21 LSES

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Social Psychological Correlates of Occupational Position

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: C. Schooler, Acting Chief, Laboratory of Socio-environmental Studies, NIMH

OTHER:	C. Schoenbach	Social Science Analyst	LSES	NIMH
	M. Kohn	Guest Researcher	LSES	NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Socio-environmental Studies

SECTION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

INSTITUTE AND LOCATION

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.90	1.90	4.00

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 object of this study is to assess the reciprocal effects of occupational conditions and psychological functioning (in particular, values, self-conceptions, social orientation, and intellectual flexibility). Structured interviews were conducted in 1964 with a sample of 3101 men, representative of all men employed in civilian occupations throughout the United States. The study was extended into a longitudinal study in 1974, with the reinterviewing of a randomly-selected one-fourth of the original sample, together with their wives and, where appropriate, one of their children. Replications of this research have been carried out in Poland and Japan.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00680-04 LSES

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Work Experiences and the Deinstitutionalized Mentally Ill

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Elliot Liebow, Guest Researcher, LSES, NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Socio-environmental Studies

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

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 exploratory, participant observation study is to examine the work experience of the deinstitutionalized mentally ill over time and to seek out ways in which job characteristics, symptoms, and social relationships interact with one another to effect the course of recovery from psychiatric disorder and reintegration into the community. Field work was carried out with residents of halfway houses, participants in community-based psychosocial and transitional work programs, and with "unattached" deinstitutionalized men and women.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00679-06 LSES

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Structural Equation Models in the Analysis of Data with Measurement Error

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Ronald J. Schoenberg, Research Sociologist	LSES	NIMH
OTHER:	C. Schooler, Acting Chief	LSES	NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Socio-environmental Studies

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.60	1.10	.50

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 work is to further develop the methods and techniques for the specification and estimation of the parameters of structural equation models of survey data that contain random and nonrandom measurement error. Included in this are methods for the identification of the models, estimation of the means of unobserved variables, the determination of model condition, and the treatment of polytomous variables.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01836-08 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

GABA/Receptors in the Central Nervous System: Biochemistry to Behavior

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	S.M. Paul	Chief	NS, NIMH
Others:	P.D. Suzdak	PRAT Fellow	NIGMS, NIMH
	A.L. Morrow	PRAT Fellow	NIGMS, NIMH
	S.I. Deutsch	PRAT Fellow	NIGMS, NIMH
	P. Skolnick	Pharmacologist	LBC, NIADDK
	R.D. Schwartz	Pharmacologist	NS, NIMH
	H. Havoundjian	Guest Researcher	LBC, NIADDK

COOPERATING UNITS *(if any)*

Laboratory of Bioorganic Chemistry, NIADDK; Section on Brain Biochemistry, NS, NIMH; Section on Molecular Pharmacology, NS, NIMH; Pharmacology Research Associate Training Program, NIGMS.

LAB/BRANCH

Section on Preclinical Studies

SECTION

NIMH, NIH, Bethesda, Maryland 20892

INSTITUTE AND LOCATION

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.0	3.5	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.)*

It is currently believed that the interaction of benzodiazepines with a specific neuronal membrane receptor initiates a series of neuronal events resulting in an enhancement of GABA-mediated chloride permeability. The latter results behaviorally in the major pharmacological actions of benzodiazepines, namely their anxiolytic, anticonvulsant, hypnotic, and muscle relaxant actions. In addition to benzodiazepines, a variety of sedative/hypnotic agents of the minor tranquilizer class (e.g. the barbiturates) appear to interact with one or more components of the benzodiazepine/GABA receptor complex, and thus the latter has been proposed as a common site of minor tranquilizer action. Several aspects of the benzodiazepine/GABA receptor complex are currently being studied, including purification of the receptor, characterization of multiple binding sites on the receptor complex which recognizes agonist, antagonists or inverse agonists. Recent work has focused on using an in vitro system for measuring GABA receptor-effector coupling in a subcellular preparation from rat brain (the synaptoneurosome). This technique has greatly facilitated studies on barbiturate and GABA receptor-mediated chloride flux and has resulted in the first reliable method for studying the function of the GABA receptor in vitro. Using this method we have studied the interaction of the popular anxiolytic/intoxicant ethyl alcohol with the GABA receptor complex and have found that ethanol and all short-chain alcohols tested are capable of stimulating this receptor and at low pharmacologically-relevant concentrations. In related studies we have identified a novel imidazobenzodiazepine, Ro15-4513, which blocks both the in vitro effects of ethanol on GABA receptor-mediated $^{36}Cl^-$ uptake as well as many of the behavioral effects of ethanol. In other studies we have examined the use of the radiolabelled benzodiazepine receptor antagonist Ro15-1788 for measuring benzodiazepine receptors in vivo. Our results have validated the suitability of this technique and have demonstrated significant effects of barbiturates, ethanol, and "stress" on benzodiazepine receptors in vivo.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01836-08 NS

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
GABA/Receptors in the Central Nervous System: Biochemistry to Behavior

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	S.M. Paul	Chief	NS, NIMH
Others:	P.D. Suzdak	PRAT Fellow	NIGMS, NIMH
	A.L. Morrow	PRAT Fellow	NIGMS, NIMH
	S.I. Deutsch	PRAT Fellow	NIGMS, NIMH
	P. Skolnick	Pharmacologist	LBC, NIADDK
	R.D. Schwartz	Pharmacologist	NS, NIMH
	H. Havoundjian	Guest Researcher	LBC, NIADDK

COOPERATING UNITS *(if any)*
Laboratory of Bioorganic Chemistry, NIADDK; Section on Brain Biochemistry, NS, NIMH; Section on Molecular Pharmacology, NS, NIMH; Pharmacology Research Associate Training Program, NIGMS.

LAB/BRANCH
Section on Preclinical Studies

SECTION
NIMH, NIH, Bethesda, Maryland 20892

INSTITUTE AND LOCATION

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.0	3.5	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.)*

It is currently believed that the interaction of benzodiazepines with a specific neuronal membrane receptor initiates a series of neuronal events resulting in an enhancement of GABA-mediated chloride permeability. The latter results behaviorally in the major pharmacological actions of benzodiazepines, namely their anxiolytic, anticonvulsant, hypnotic, and muscle relaxant actions. In addition to benzodiazepines, a variety of sedative/hypnotic agents of the minor tranquilizer class (e.g. the barbiturates) appear to interact with one or more components of the benzodiazepine/GABA receptor complex, and thus the latter has been proposed as a common site of minor tranquilizer action. Several aspects of the benzodiazepine/GABA receptor complex are currently being studied, including purification of the receptor, characterization of multiple binding sites on the receptor complex which recognizes agonist, antagonists or inverse agonists. Recent work has focused on using an in vitro system for measuring GABA receptor-effector coupling in a subcellular preparation from rat brain (the synaptoneurosome). This technique has greatly facilitated studies on barbiturate and GABA receptor-mediated chloride flux and has resulted in the first reliable method for studying the function of the GABA receptor in vitro. Using this method we have studied the interaction of the popular anxiolytic/intoxicant ethyl alcohol with the GABA receptor complex and have found that ethanol and all short-chain alcohols tested are capable of stimulating this receptor and at low pharmacologically-relevant concentrations. In related studies we have identified a novel imidazobenzodiazepine, Ro15-4513, which blocks both the in vitro effects of ethanol on GABA receptor-mediated $^{36}Cl^-$ uptake as well as many of the behavioral effects of ethanol. In other studies we have examined the use of the radiolabelled benzodiazepine receptor antagonist Ro15-1788 for measuring benzodiazepine receptors in vivo. Our results have validated the suitability of this technique and have demonstrated significant effects of barbiturates, ethanol, and "stress" on benzodiazepine receptors in vivo.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02186-04 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Brain Recognition Sites for Stimulants and Antidepressants: Relationship to Pharmacological Activity

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	S.M. Paul	Chief	NS, NIMH
Others:	P. Skolnick	Pharmacologist	LBC, NIADDK
	J.N. Crawley	Senior Staff Fellow	NS, NIMH
	E. Lestringant	Guest Researcher	NS, NIMH
	G. Muscettola	Visiting Associate	NS, NIMH

COOPERATING UNITS *(if any)*

Laboratory of Bioorganic Chemistry, NIADDK; Section on Molecular Pharmacology, NS, NIMH;

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Preclinical Studies

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.0	3.5	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.)*

Recognition sites for a variety of psychotherapeutic drugs have been identified in the central nervous system. Over the past several years we have attempted to identify recognition sites for other common psychotropic drugs including tricyclic antidepressants and the psychomotor stimulants, amphetamine and methylphenidate. In each case saturable, and stereospecific binding sites have been delineated; and for amphetamine and methylphenidate relatively good correlations have been observed between the affinities of a series of analogues in vitro and at least some of the pharmacological properties of these agents. Recent work has shown that the [^{3}H] (+)-amphetamine binding site in hypothalamic membranes is sensitive to circulating levels of blood glucose. Hypoglycemia decreases, and hyperglycemia increases, the number of [^{3}H] (+)-amphetamine binding sites in hypothalamic membranes respectively. Furthermore, these changes seemed to be coupled to the activity of (Na^+ K^+) (ATPase; and there is a good correlation between the changes in [^{3}H] (+)-amphetamine and [^{3}H]-ouabain binding both in vivo and in vitro. More recent studies have shown that [^{3}H]-mazindol a chemically unrelated anorectic/psychostimulant also can be used to label the [^{3}H] (+)-amphetamine recognition site and that there is a good correlation between the inhibition of [^{3}H]-mazindol binding by a series of phenylethylamines and their anorectic potencies in rats. These data suggest the existence of a membrane-bound receptor complex capable of "sensing" circulating glucose concentration and in regulating both glucostatic ingestive behavior and perhaps some aspects of the central regulation of energy metabolism. More recent work has demonstrated that genetically obese mice (ob/ob) have an abnormality in this system and fail to respond to glucoprivic feeding signals.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02186-04 NS

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Brain Recognition Sites for Stimulants and Antidepressants: Relationship to Pharmacological Activity

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	S.M. Paul	Chief	NS, NIMH
Others:	P. Skolnick	Pharmacologist	LBC, NIADDK
	J.N. Crawley	Senior Staff Fellow	NS, NIMH
	E. Lestringant	Guest Researcher	NS, NIMH
	G. Muscettola	Visiting Associate	NS, NIMH

COOPERATING UNITS *(if any)*
Laboratory of Bioorganic Chemistry, NIADDK; Section on Molecular Pharmacology, NS, NIMH;

LAB/BRANCH
Clinical Neuroscience Branch

SECTION
Section on Preclinical Studies

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.0	3.5	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.)*

Recognition sites for a variety of psychotherapeutic drugs have been identified in the central nervous system. Over the past several years we have attempted to identify recognition sites for other common psychotropic drugs including tricyclic antidepressants and the psychomotor stimulants, amphetamine and methylphenidate. In each case saturable, and stereospecific binding sites have been delineated; and for amphetamine and methylphenidate relatively good correlations have been observed between the affinities of a series of analogues in vitro and at least some of the pharmacological properties of these agents. Recent work has shown that the [^{3}H] (+)-amphetamine binding site in hypothalamic membranes is sensitive to circulating levels of blood glucose. Hypoglycemia decreases, and hyperglycemia increases, the number of [^{3}H] (+)-amphetamine binding sites in hypothalamic membranes respectively. Furthermore, these changes seemed to be coupled to the activity of (Na^+ K^+) (ATPase; and there is a good correlation between the changes in [^{3}H] (+)-amphetamine and [^{3}H]-ouabain binding both in vivo and in vitro. More recent studies have shown that [^{3}H]-mazindol a chemically unrelated anorectic/psychostimulant also can be used to label the [^{3}H] (+)-amphetamine recognition site and that there is a good correlation between the inhibition of [^{3}H]-mazindol binding by a series of phenylethylamines and their anorectic potencies in rats. These data suggest the existence of a membrane-bound receptor complex capable of "sensing" circulating glucose concentration and in regulating both glucostatic ingestive behavior and perhaps some aspects of the central regulation of energy metabolism. More recent work has demonstrated that genetically obese mice (ob/ob) have an abnormality in this system and fail to respond to glucoprivic feeding signals.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02340-01 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)* Biochemical and Clinical Studies of Gaucher Disease and Other Neurogenetic Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	E.I. Ginns	Head, Molecular Neurogenetics Unit	NS, NIMH
Others:	S. Tsuji	Visiting Fellow	NS, NIMH
	B. Martin	Visiting Scientist	NS, NIMH
	J. Sidbury	Chief, Section on Human Biochem. Genetics	HGB, NICHD
	B. Martin	Guest Researcher	NS, NIMH
	M. LaMarca	Guest Researcher	NS, NIMH
	S. Winfield	Microbiologist	NS, NIMH
	B. Stubblefield	Biologist	NS, NIMH

COOPERATING UNITS *(if any)* Human Genetics Branch, National Institute of Child Health and Human Development; Interinstitute Genetics Program, NIH; Laboratory of Molecular Genetics, NINCDS; Massachussets General Hospital, Boston, MA; Children's Hospital, Los Angeles, CA

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Molecular Neurogenetics Unit, Preclinical Studies Section

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.6	0.4	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.)*

The clinical study of neurogenetic diseases provides the foundation for the development of techniques for improved diagnosis and strategies for therapy. This goal is greatly facilitated by having a comprehensive knowledge of the biochemistry and clinical heterogeneity of the disorder. Gaucher disease, the most common sphingolipidosis, has a high priority as a model for gaining insight into this group of neurogenetic disorders because of the occurrence of both neuronopathic and non-neuronopathic phenotypes as well as the broad spectrum of clinical diversity within the major types of the disorder. Once the pathophysiologic mechanisms of systemic involvement are understood, the therapy of nervous system dysfunction may be more rationally approached. Basic research on glucocerebrosidase, the enzyme deficient in Gaucher disease, has generated a more detailed understanding of the structure, biosynthesis, intracellular routing, and turnover of the enzyme. These studies will complement other studies within our branch focusing on the investigation of the potential and efficacy of gene transfer as a therapeutic approach.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02340-01 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)* Biochemical and Clinical Studies of Gaucher Disease and Other Neurogenetic Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	E.I. Ginns	Head, Molecular Neurogenetics Unit	NS, NIMH
Others:	S. Tsuji	Visiting Fellow	NS, NIMH
	B. Martin	Visiting Scientist	NS, NIMH
	J. Sidbury	Chief, Section on Human Biochem. Genetics	HGB, NICHD
	B. Martin	Guest Researcher	NS, NIMH
	M. LaMarca	Guest Researcher	NS, NIMH
	S. Winfield	Microbiologist	NS, NIMH
	B. Stubblefield	Biologist	NS, NIMH

COOPERATING UNITS *(if any)* Human Genetics Branch, National Institute of Child Health and Human Development; Interinstitute Genetics Program, NIH; Laboratory of Molecular Genetics, NINCDS; Massachussets General Hospital, Boston, MA; Children's Hospital, Los Angeles, CA

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Molecular Neurogenetics Unit, Preclinical Studies Section

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.6	0.4	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.)*

The clinical study of neurogenetic diseases provides the foundation for the development of techniques for improved diagnosis and strategies for therapy. This goal is greatly facilitated by having a comprehensive knowledge of the biochemistry and clinical heterogeneity of the disorder. Gaucher disease, the most common sphingolipidosis, has a high priority as a model for gaining insight into this group of neurogenetic disorders because of the occurrence of both neuronopathic and non-neuronopathic phenotypes as well as the broad spectrum of clinical diversity within the major types of the disorder. Once the pathophysiologic mechanisms of systemic involvement are understood, the therapy of nervous system dysfunction may be more rationally approached. Basic research on glucocerebrosidase, the enzyme deficient in Gaucher disease, has generated a more detailed understanding of the structure, biosynthesis, intracellular routing, and turnover of the enzyme. These studies will complement other studies within our branch focusing on the investigation of the potential and efficacy of gene transfer as a therapeutic approach.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02341-01 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Correction of Inherited Enzyme Deficiencies by Gene Transfer

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	E.I. Ginns	Head, Molecular Neurogenetics Unit	NS, NIMH
Others:	B. Martin	Visiting Scientist	NS, NIMH
	S. Tsuji	Visiting Fellow	NS, NIMH
	B. Stubblefield	Biologist	NS, NIMH
	M. LaMarca	Guest Researcher	NS, NIMH
	S. Winfield	Microbiologist	NS, NIMH
	B. Martin	Guest Researcher	NS, NIMH
	W. Eliason	Guest Researcher	NS, NIMH

COOPERATING UNITS *(if any)*

Laboratory of Molecular Genetics, NINCDS; Center for Cancer Research, MIT and Whitehead Institute for Biomedical Research, Boston, MA; Children's Hospital, Los Angeles, CA

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Molecular Neurogenetics Unit, Preclinical Studies Section

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.6	0.6	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 isolation and characterization of proteins involved in the pathogenesis of neurogenetic disorders has permitted the isolation of cDNA and genomic DNA that can be used to investigate the correction of inherited enzyme deficiencies using recombinant DNA techniques, specifically somatic cell gene transfer. Particularly suited for initial attempts at gene therapy are those disorders (such as Gaucher disease, the most common sphingolipidosis) in which the manifestations of the disorder are due to abnormalities of hematopoietic cells, in this case, the macrophage. In this instance the transfer of normal genes to bone marrow progenitor cells is a rationale therapeutic approach. Using the lysosomal disorder Gaucher disease as a model, we have been successful in utilizing retroviral vectors to transfer and express human glucocerebrosidase in host mouse and Gaucher cell lines. The complete correction of glucocerebrosidase activity in Type 2 Gaucher fibroblasts in culture has provided the impetus for evaluation of retroviral mediated somatic cell gene transfer of the glucocerebrosidase gene into mice by bone marrow transplantation. The initial goal of this research is the application of these recombinant DNA therapeutic strategies to the non-neuronopathic phenotypes. When our understanding of the pathogenetic mechanisms of inherited neurological and psychiatric diseases improves and when retroviral-mediated expression of genes in specific tissues and cells become more predictable, we can begin to investigate the potential usefulness of gene therapy for treatment of selected nervous system disorders.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02341-01 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Correction of Inherited Enzyme Deficiencies by Gene Transfer

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PI:	E.I. Ginns	Head, Molecular Neurogenetics Unit	NS, NIMH
Others:	B. Martin	Visiting Scientist	NS, NIMH
	S. Tsuji	Visiting Fellow	NS, NIMH
	B. Stubblefield	Biologist	NS, NIMH
	M. LaMarca	Guest Researcher	NS, NIMH
	S. Winfield	Microbiologist	NS, NIMH
	B. Martin	Guest Researcher	NS, NIMH
	W. Eliason	Guest Researcher	NS, NIMH

COOPERATING UNITS *(if any)*

Laboratory of Molecular Genetics, NINCDS; Center for Cancer Research, MIT and Whitehead Institute for Biomedical Research, Boston, MA; Children's Hospital, Los Angeles, CA

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Molecular Neurogenetics Unit, Preclinical Studies Section

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.6	0.6	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 isolation and characterization of proteins involved in the pathogenesis of neurogenetic disorders has permitted the isolation of cDNA and genomic DNA that can be used to investigate the correction of inherited enzyme deficiencies using recombinant DNA techniques, specifically somatic cell gene transfer. Particularly suited for initial attempts at gene therapy are those disorders (such as Gaucher disease, the most common sphingolipidosis) in which the manifestations of the disorder are due to abnormalities of hematopoietic cells, in this case, the macrophage. In this instance the transfer of normal genes to bone marrow progenitor cells is a rationale therapeutic approach. Using the lysosomal disorder Gaucher disease as a model, we have been successful in utilizing retroviral vectors to transfer and express human glucocerebrosidase in host mouse and Gaucher cell lines. The complete correction of glucocerebrosidase activity in Type 2 Gaucher fibroblasts in culture has provided the impetus for evaluation of retroviral mediated somatic cell gene transfer of the glucocerebrosidase gene into mice by bone marrow transplantation. The initial goal of this research is the application of these recombinant DNA therapeutic strategies to the non-neuronopathic phenotypes. When our understanding of the pathogenetic mechanisms of inherited neurological and psychiatric diseases improves and when retroviral-mediated expression of genes in specific tissues and cells become more predictable, we can begin to investigate the potential usefulness of gene therapy for treatment of selected nervous system disorders.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02342-01 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Gene Regulation within the Nervous System

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	E.I. Ginns	Head, Molecular Neurogenetics Unit	NS, NIMH
Others:	B. Martin	Visiting Scientist	NS, NIMH
	S. Tsuji	Visiting Fellow	NS, NIMH
	S. Winfield	Microbiologist	NS, NIMH
	P. Marangos	Unit on Neurochemistry	BPB, NIMH
	D. Schmeckel	Neurology Department	VAMC
	J. Polak	Royal Post-Graduate Medical School, London	
	J. Hozier	Medical Genetics	FIT

COOPERATING UNITS *(if any)*

Unit on Neurochemistry, Biological Psychiatry Branch, NIMH; Veterans Administration Medical Center, Durham, NC; Royal Post-Graduate Medicl School, London, England; Florida Institute of Technology, Melbourne, FL

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Molecular Neurogenetics Unit, Preclinical Studies Section

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.7	0.4	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.)*

We approached the cell-specific and developmentally regulated expression of proteins within the nervous system using the neuron specific (NSE) and non-neuronal (NNE) enolase isozymes as a model (refer to Z01 MH 01831-10 BP). Human brain cDNA and genomic DNA libraries were constructed so that the genes for these and other brain specific proteins could be isolated and characterized. Using both antibodies and oligonucleotide probes, cDNAs for both human NSE and NNE have been isolated and sequenced. Employing unique regions of these cDNA clones as probes, the developmentally and cell-specific regulated appearance of mRNA for each of these proteins can be investigated using in-situ hydridization. The human chromosome loci for each of these isozymes will be identified. In addition, the isolation of human genomic clones for each of these proteins should provide information on the regulation of expression of neuron and glial specific proteins during cell differentiation of the human nervous system in normal and disease states. The normal specificity of NSE for neural derived cell lines and the availability of specific DNA probes for NSE should provide a useful approach to the characterization of neural derived normal and tumor cell lineages.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02342-01 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Gene Regulation within the Nervous System

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	E.I. Ginns	Head, Molecular Neurogenetics Unit	NS, NIMH
Others:	B. Martin	Visiting Scientist	NS, NIMH
	S. Tsuji	Visiting Fellow	NS, NIMH
	S. Winfield	Microbiologist	NS, NIMH
	P. Marangos	Unit on Neurochemistry	BPB, NIMH
	D. Schmeckel	Neurology Department	VAMC
	J. Polak	Royal Post-Graduate Medical School, London	
	J. Hozier	Medical Genetics	FIT

COOPERATING UNITS *(if any)*

Unit on Neurochemistry, Biological Psychiatry Branch, NIMH; Veterans Administration Medical Center, Durham, NC; Royal Post-Graduate Medicl School, London, England; Florida Institute of Technology, Melbourne, FL

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Molecular Neurogenetics Unit, Preclinical Studies Section

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.7	0.4	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.)*

We approached the cell-specific and developmentally regulated expression of proteins within the nervous system using the neuron specific (NSE) and non-neuronal (NNE) enolase isozymes as a model (refer to Z01 MH 01831-10 BP). Human brain cDNA and genomic DNA libraries were constructed so that the genes for these and other brain specific proteins could be isolated and characterized. Using both antibodies and oligonucleotide probes, cDNAs for both human NSE and NNE have been isolated and sequenced. Employing unique regions of these cDNA clones as probes, the developmentally and cell-specific regulated appearance of mRNA for each of these proteins can be investigated using in-situ hydridization. The human chromosome loci for each of these isozymes will be identified. In addition, the isolation of human genomic clones for each of these proteins should provide information on the regulation of expression of neuron and glial specific proteins during cell differentiation of the human nervous system in normal and disease states. The normal specificity of NSE for neural derived cell lines and the availability of specific DNA probes for NSE should provide a useful approach to the characterization of neural derived normal and tumor cell lineages.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02343-01 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Molecular Genetics of Inherited Neurologic and Psychiatric Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	S. Tsuji	Visiting Fellow	NS, NIMH
Others:	E.I. Ginns	Head, Molecular Neurogenetics Unit	NS, NIMH
	S.M. Paul	Chief, Clinical Neuroscience Branch	NS, NIMH
	D. Pickar	Chief, Section on Clinical Studies	NS, NIMH
	B. Martin	Visiting Scientist	NS, NIMH
	B. Stubblefield	Biologist	NS, NIMH
	S. Winfield	Microbiologist	NS, NIMH
	P. Choudary	Staff Fellow	LMG, NINCDS

COOPERATING UNITS *(if any)*

Laboratory of Molecular Genetics, NINCDS; Pediatrics Department, Johns Hopkins School of Medicine, Baltimore, MD; Children's Hospital, Los Angeles, CA; Florida Institute of Technology, Melbourne, FL

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Molecular Neurogenetics Unit, Preclinical Studies Section

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.6	0.9	0.7

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.)*

We approached the characterization of the mutations responsible for inherited neurological or psychiatric disorders by studying the gene organization of specific proteins that might have a role in the pathogenesis of the clinical manifestations. Using the inherited lysosomal storage disorders, Gaucher disease and Fabry disease, as models, we demonstrated that the phenotypic heterogeneity seen within these inherited disorders is a consequence of different mutations, each affecting protein activity and influencing the processing, compartmentalization and/or stability of the protein. Recombinant DNA techniques have been used to elucidate the structure of the gene for the proteins involved in these disorders. Restriction fragment length polymorphisms (RFLPs) have been identified that are useful for the identification of a mutation in Gaucher disease which frequently occurs in neuronopathic phenotypes. Northern blot analysis provides further details of the structure of the normal and mutant genes. The molecular mechanisms leading to nervous system involvement in these disorders have also been investigated. The results of this research should provide a more rational foundation for the diagnosis and formulation of therapeutic strategies for these inherited disorders.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02343-01 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Molecular Genetics of Inherited Neurologic and Psychiatric Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	S. Tsuji	Visiting Fellow	NS, NIMH
Others:	E.I. Ginns	Head, Molecular Neurogenetics Unit	NS, NIMH
	S.M. Paul	Chief, Clinical Neuroscience Branch	NS, NIMH
	D. Pickar	Chief, Section on Clinical Studies	NS, NIMH
	B. Martin	Visiting Scientist	NS, NIMH
	B. Stubblefield	Biologist	NS, NIMH
	S. Winfield	Microbiologist	NS, NIMH
	P. Choudary	Staff Fellow	LMG, NINCDS

COOPERATING UNITS *(if any)*

Laboratory of Molecular Genetics, NINCDS; Pediatrics Department, Johns Hopkins School of Medicine, Baltimore, MD; Children's Hospital, Los Angeles, CA; Florida Institute of Technology, Melbourne, FL

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Molecular Neurogenetics Unit, Preclinical Studies Section

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.6	0.9	0.7

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.)*

We approached the characterization of the mutations responsible for inherited neurological or psychiatric disorders by studying the gene organization of specific proteins that might have a role in the pathogenesis of the clinical manifestations. Using the inherited lysosomal storage disorders, Gaucher disease and Fabry disease, as models, we demonstrated that the phenotypic heterogeneity seen within these inherited disorders is a consequence of different mutations, each affecting protein activity and influencing the processing, compartmentalization and/or stability of the protein. Recombinant DNA techniques have been used to elucidate the structure of the gene for the proteins involved in these disorders. Restriction fragment length polymorphisms (RFLPs) have been identified that are useful for the identification of a mutation in Gaucher disease which frequently occurs in neuronopathic phenotypes. Northern blot analysis provides further details of the structure of the normal and mutant genes. The molecular mechanisms leading to nervous system involvement in these disorders have also been investigated. The results of this research should provide a more rational foundation for the diagnosis and formulation of therapeutic strategies for these inherited disorders.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02344-01 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Neuropsychiatric Disorders: Protein Structure-Activity Studies

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	B. Martin	Visiting Scientist	NS, NIMH
Others:	E.I. Ginns	Head, Molecular Neurogenetics Unit	NS, NIMH
	D. Merkle-Lehman	Guest Researcher	NS, NIMH
	W. Eliason	Guest Researcher	NS, NIMH
	P. Marangos	Unit on Neurochemistry	BPB, NIMH
	J. Barranger	Division of Genetics, Children's Hospital, CA	
	L. Possani	Free University of Mexico, Mexico	

COOPERATING UNITS *(if any)*

Unit on Neurochemistry, Biological Psychiatry Branch, NIMH; Children's Hospital, Los Angeles, CA; Free University of Mexico, Mexico

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Molecular Neurogenetics Unit, Preclinical Studies Section

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

This research is part of an effort to better understand the molecular mechanisms underlying human nervous system development and function, as well as the pathogenesis of certain neurogenetic disorders. Our studies have focused on structural and active site properties of the human non-neuronal and neuron specific enolases, lysosomal hydrolases (glucocerebro- sidase and α-galactosidase A), other enzymes (particularly those peptides and proteins that interact with excitable membranes), and venom toxins. Proteins are purified from both human and animal tissues using affinity chromatography, electrophoretic separation, and high performance liquid chromatography. Using microsequencing techniques, the complete amino acid sequence of glucocerebro-sidase, and major portions of sequences for the neuronal and non-neuronal enolases, venom toxins, and α-galactosidase A have been obtained. Peptide maps of both normal and mutant proteins are generated using chemical (cyanogen bromide) and enzymatic (trypsin, thermolysin, V8 protease) cleavage. The identification of carbohydrate attachment sites, sulfhydryl residues, and intra-chain disulfide residues is used to predict protein structure. Alkylating agents and enzyme inhibitors are used to define active sites. From the primary protein sequence, hydrophobic and hydrophilic domains of the protein are identified.

Information obtained from these protein structure studies permits the design of oligonucleotides and peptides that are synthesized for collaborative research involving antibody production, cDNA cloning, DNA sequence analysis and in vitro mutagenesis.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02344-01 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Neuropsychiatric Disorders: Protein Structure-Activity Studies

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	B. Martin	Visiting Scientist	NS, NIMH
Others:	E.I. Ginns	Head, Molecular Neurogenetics Unit	NS, NIMH
	D. Merkle-Lehman	Guest Researcher	NS, NIMH
	W. Eliason	Guest Researcher	NS, NIMH
	P. Marangos	Unit on Neurochemistry	BPB, NIMH
	J. Barranger	Division of Genetics, Children's Hospital, CA	
	L. Possani	Free University of Mexico, Mexico	

COOPERATING UNITS *(if any)*

Unit on Neurochemistry, Biological Psychiatry Branch, NIMH; Children's Hospital, Los Angeles, CA; Free University of Mexico, Mexico

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Molecular Neurogenetics Unit, Preclinical Studies Section

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

This research is part of an effort to better understand the molecular mechanisms underlying human nervous system development and function, as well as the pathogenesis of certain neurogenetic disorders. Our studies have focused on structural and active site properties of the human non-neuronal and neuron specific enolases, lysosomal hydrolases (glucocerebro- sidase and α-galactosidase A), other enzymes (particularly those peptides and proteins that interact with excitable membranes), and venom toxins. Proteins are purified from both human and animal tissues using affinity chromatography, electrophoretic separation, and high performance liquid chromatography. Using microsequencing techniques, the complete amino acid sequence of glucocerebro-sidase, and major portions of sequences for the neuronal and non-neuronal enolases, venom toxins, and α-galactosidase A have been obtained. Peptide maps of both normal and mutant proteins are generated using chemical (cyanogen bromide) and enzymatic (trypsin, thermolysin, V8 protease) cleavage. The identification of carbohydrate attachment sites, sulfhydryl residues, and intra-chain disulfide residues is used to predict protein structure. Alkylating agents and enzyme inhibitors are used to define active sites. From the primary protein sequence, hydrophobic and hydrophilic domains of the protein are identified.

Information obtained from these protein structure studies permits the design of oligonucleotides and peptides that are synthesized for collaborative research involving antibody production, cDNA cloning, DNA sequence analysis and in vitro mutagenesis.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00112-09 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Endorphin Research in Mental Illness

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D. Pickar	Chief, Section on Clinical Studies	NS, NIMH
Others:	G.A. Roy	Visiting Associate	NS, NIMH
	O.M. Wolkowitz	Medical Staff Fellow	NS, NIMH
	A.F. Breier	Medical Staff Fellow	NS, NIMH
	T.N. Wise	Chief of Psychiatry, Fairfax Hospital	

COOPERATING UNITS *(if any)*

Fairfax Hospital, Fairfax, VA

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.0	2.5	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.)*

This project has studied the role of the endogenous opioid system (EOS) in humans. Current studies have focused on EOS involvement in eating behavior. We have observed that naloxone significantly reduces food consumption (25%) in obese individuals. Current studies involve the administration of long-acting oral opiate antagonists in schizophrenic patients.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00112-09 NS

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October 1, 1985 to September 30, 1986

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Others:	G.A. Roy	Visiting Associate	NS, NIMH
	O.M. Wolkowitz	Medical Staff Fellow	NS, NIMH
	A.F. Breier	Medical Staff Fellow	NS, NIMH
	T.N. Wise	Chief of Psychiatry, Fairfax Hospital	

COOPERATING UNITS *(if any)*

Fairfax Hospital, Fairfax, VA

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.0	2.5	1.5

CHECK APPROPRIATE BOX(ES)

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

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

This project has studied the role of the endogenous opioid system (EOS) in humans. Current studies have focused on EOS involvement in eating behavior. We have observed that naloxone significantly reduces food consumption (25%) in obese individuals. Current studies involve the administration of long-acting oral opiate antagonists in schizophrenic patients.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02181-04 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Neurobiology of Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D. Pickar	Chief, Section on Clinical Studies	NS, NIMH
Others:	S.M. Paul	Chief	NS, NIMH
	A.F. Breier	Medical Staff Fellow	NS, NIMH
	A.R. Doran	Medical Staff Fellow	NS, NIMH
	J.R. Kelsoe	Medical Staff Fellow	NS, NIMH
	P.B. Lucas	NRSA Fellow	NS, NIMH
	O.M. Wolkowitz	Medical Staff Fellow	NS, NIMH
	J.L. Schreiber	Social Worker	NS, NIMH

COOPERATING UNITS *(if any)*

Laboratory of Psychology and Psychopathology, NIMH; Neuropsychiatry Branch, St. Elizabeths Hospital, NIMH

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.0	3.0	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 aim of this project is to gain a greater understanding of the psychobiology of schizophrenia and to develop improved strategies for its treatment. An important goal is the understanding of the mechanism of action of neuroleptic drugs. We have observed that neuroleptic-induced time-dependent decrease in levels of plasma homovanillic acid (HVA), a major dopamine metabolite, correlates with antipsychotic drug response, suggesting that slow to develop changes in dopamine turnover may underlie the antipsychotic action of neuroleptics. The origin of this clinically relevant HVA "signal" (peripheral or central CNS) is being investigated by a strategy in which peripherally derived HVA is reduced by the administration of debrisoquin, a MAO inhibitor which does not enter the CNS. In a double-blind, treatment trial, we have observed significant reduction in psychosis when alprazolam is added to neuroleptic treatment. These data contrast with the negative results found when the calcium channel blocker, verapamil, was administered to otherwise medication-free schizophrenic patients. In studies using computerized tomography imaging techniques, findings continue to support structural abnormality in the prefrontal cortex of schizophrenic patients. Magnetic resonance imaging (MRI) techniques are currently being employed to pursue structural abnormalities in brains of schizophrenic patients. The proposed course of study highlights the pharmacotherapy of schizophrenia, including the use of levels of plasma HVA as a marker for antipsychotic response and the augmentation of neuroleptic response using triazolobenzodiazepines.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02181-04 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D. Pickar	Chief, Section on Clinical Studies	NS, NIMH
Others:	S.M. Paul	Chief	NS, NIMH
	A.F. Breier	Medical Staff Fellow	NS, NIMH
	A.R. Doran	Medical Staff Fellow	NS, NIMH
	J.R. Kelsoe	Medical Staff Fellow	NS, NIMH
	P.B. Lucas	NRSA Fellow	NS, NIMH
	O.M. Wolkowitz	Medical Staff Fellow	NS, NIMH
	J.L. Schreiber	Social Worker	NS, NIMH

COOPERATING UNITS *(if any)*

Laboratory of Psychology and Psychopathology, NIMH; Neuropsychiatry Branch, St. Elizabeths Hospital, NIMH

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.0	3.0	1.0

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☒ (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.)*

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02184-04 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Neurobiology of Depression

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D. Pickar	Chief, Section on Clinical Studies	NS, NIMH
Others:	S.M. Paul	Chief	NS, NIMH
	G.A. Roy	Visiting Associate	NS, NIMH
	O.M. Wolkowitz	Medical Staff Fellow	NS, NIMH
	A.R. Doran	Medical Staff Fellow	NS, NIMH
	A.F. Breier	Medical Staff Fellow	NS, NIMH
	W.Z. Potter	Chief, Unit on Clinical Psychopharmacology	LCS, NIMH
	D. Rubinow	Chief, Unit on Peptide Studies	BPB, NIMH

COOPERATING UNITS *(if any)*

Laboratory of Clinical Science, Biological Psychiatry Branch and Laboratory of Neurochemistry, NIMH

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.0	3.0	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 aim of this study is to investigate selected areas of the neurobiology of depression. In previous studies, we have observed that abnormality of noradrenergic and HPA axis dysfunction occur together in seriously depressed patients. We have pursued the study of the role of corticosteroids in depressive illness by examining the effect of exogenous steroid administration. We have found that orally administered dexamethasone produces selective effects on catecholamine function in depressed patients; in contrast to normal controls, depressed patients, particularly those with psychotic features, showed a significant dexamethasone-induced increase in plasma MHPG and a decrease in plasma HVA. These data suggesting abnormal corticosteroid-catecholamine interactions in depression are consistent with the possibility that hypercortisolemia itself may produce or enhance some of the biochemical changes and/or behavioral signs of depression. In a double-blind study of orally administered prednisone (80 mg/day x 5 days) to normal volunteers, we have further investigated steroid effects on the central nervous system. The relationship between stress, steroids, and mood, has been pursued in an experiment in which identical amounts of escapable and inescapable aversive noise stimuli are presented to subjects. Preliminary results suggest that inescapable but not escapable "stress" produces correlated mood and neuroendocrine response. This paradigm holds promise for examining not only stress response in normal subjects but also as a model of depression and as a tool to investigate biological diathesis in patients with current depressive illness and in subjects at risk for depression.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02184-04 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Neurobiology of Depression

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D. Pickar	Chief, Section on Clinical Studies	NS, NIMH
Others:	S.M. Paul	Chief	NS, NIMH
	G.A. Roy	Visiting Associate	NS, NIMH
	O.M. Wolkowitz	Medical Staff Fellow	NS, NIMH
	A.R. Doran	Medical Staff Fellow	NS, NIMH
	A.F. Breier	Medical Staff Fellow	NS, NIMH
	W.Z. Potter	Chief, Unit on Clinical Psychopharmacology	LCS, NIMH
	D. Rubinow	Chief, Unit on Peptide Studies	BPB, NIMH

COOPERATING UNITS *(if any)*

Laboratory of Clinical Science, Biological Psychiatry Branch and Laboratory of Neurochemistry, NIMH

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.0	3.0	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 aim of this study is to investigate selected areas of the neurobiology of depression. In previous studies, we have observed that abnormality of noradrenergic and HPA axis dysfunction occur together in seriously depressed patients. We have pursued the study of the role of corticosteroids in depressive illness by examining the effect of exogenous steroid administration. We have found that orally administered dexamethasone produces selective effects on catecholamine function in depressed patients; in contrast to normal controls, depressed patients, particularly those with psychotic features, showed a significant dexamethasone-induced increase in plasma MHPG and a decrease in plasma HVA. These data suggesting abnormal corticosteroid-catecholamine interactions in depression are consistent with the possibility that hypercortisolemia itself may produce or enhance some of the biochemical changes and/or behavioral signs of depression. In a double-blind study of orally administered prednisone (80 mg/day x 5 days) to normal volunteers, we have further investigated steroid effects on the central nervous system. The relationship between stress, steroids, and mood, has been pursued in an experiment in which identical amounts of escapable and inescapable aversive noise stimuli are presented to subjects. Preliminary results suggest that inescapable but not escapable "stress" produces correlated mood and neuroendocrine response. This paradigm holds promise for examining not only stress response in normal subjects but also as a model of depression and as a tool to investigate biological diathesis in patients with current depressive illness and in subjects at risk for depression.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02187-03 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Diazepam Infusions as a Measure of Benzodiazepine Receptor Sensitivity in Humans

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D.W. Hommer	Staff Psychiatrist	NS, NIMH
Others:	S.M. Paul	Chief	NS, NIMH
	D. Pickar	Chief, Section on Clinical Studies	NS, NIMH
	O.M. Wolkowitz	Medical Staff Fellow	NS, NIMH
	A. Breier	Medical Staff Fellow	NS, NIMH
	H. Weingartner	Chief, Section on Psychopathology	LPP, NIMH
	D. Rubinow	Chief, Unit on Peptide Studies	BPB, NIMH
	V. Matsuo	Physiologist	IR, NEI

COOPERATING UNITS *(if any)*

Laboratory of Psychology and Psychopathology, NIMH; Biological Psychiatry Branch, NIMH; Intramural Research, National Eye Institute; Alcohol Intramural Research Program, National Institute of Alcohol Abuse and Alcoholism; Tufts University

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	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.)*

Increasing doses of the benzodiazepine, diazepam, or placebo were administered to normal volunteers, drug-free alcoholic inpatients or patients with premenstral syndrome who were participating in a clinical trial of the benzodiazepine alprazolam in a double-blind, cross-over study. In one series of experiments, subjects were pretreated with either placebo or the benzodiazepine antagonist, Ro-15-1788. In another series, subjects were pretreated with placebo or a high or low dose of caffeine. Following each dose of drug saccadic eye velocity, diazepam blood levels, plasma cortisol, and growth hormone were measured and self-ratings of anxiety and sedation were performed. After every other dose cognitive testing of memory and attention was performed. The effects of diazepam on these variables was quantified and diazepam dose response curves constructed. These dose response curves provide a measure of benzodiazepine receptor sensitivity in humans, as well as an evaluation of the ability of specific and nonspecific antagonists to block the actions of benzodiazepines. The studies involving patients participating the the clinical trial of alprazolam will allow an examination of the effects of acute and chronic benzodiazepine treatment on receptor sensitivity.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02187-03 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

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PI:	D.W. Hommer	Staff Psychiatrist	NS, NIMH
Others:	S.M. Paul	Chief	NS, NIMH
	D. Pickar	Chief, Section on Clinical Studies	NS, NIMH
	O.M. Wolkowitz	Medical Staff Fellow	NS, NIMH
	A. Breier	Medical Staff Fellow	NS, NIMH
	H. Weingartner	Chief, Section on Psychopathology	LPP, NIMH
	D. Rubinow	Chief, Unit on Peptide Studies	BPB, NIMH
	V. Matsuo	Physiologist	IR, NEI

COOPERATING UNITS *(if any)*

Laboratory of Psychology and Psychopathology, NIMH; Biological Psychiatry Branch, NIMH; Intramural Research, National Eye Institute; Alcohol Intramural Research Program, National Institute of Alcohol Abuse and Alcoholism; Tufts University

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.7	1.2	0.5

CHECK APPROPRIATE BOX(ES)

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

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

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02188-03 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Biological Studies of Borderline Personality Disorder

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D.L. Gardner	Staff Psychiatrist	NS, NIMH
Others:	R.W. Cowdry	Clinical Director	NIMH
	K. O'Leary	Social Worker (Research)	OD, DIRP, NIMH
	R.L. Post	Chief	BP, NIMH
	M. Kling	Medical Staff Fellow	BP, NIMH
	R. Coppola	Senior Engineer	LPP, NIMH
	D. Pickar	Chief, Sec on Clinical Studies	NS, NIMH
	P. Lucas	Clinical Fellow, NRSA Fellow	NS, NIMH

COOPERATING UNITS *(if any)*

Office of the Director, Division of Intramural Research Programs, NIMH; Biological Psychiatry Branch, NIMH; Laboratory of Psychology and Psychopathology, NIMH

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.7	1.5	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.)*

Patients with borderline personality disorder and rejection-sensitive dysphoria participated in a program of clinical and biological evaluation. In addition to labile moods and behavioral dyscontrol, a high incidence of discrete major depressive episodes has been observed. Signs of neurophysiological dysfunction included a high incidence of psychomotor-psychosensory symptoms and a high incidence of neurological soft signs. Neuropsychological testing revealed a pattern of poor performance in tests of tonal memory, a function usually linked to the right temporal lobe. Procaine infusions frequently produced dysphorias similar to those occurring naturally, but generally produced only physiological symptoms in normal controls. Procaine activated a high frequency band of EEG activity over the temporal lobes in association with the dysphorias. Naloxone infusions are being performed to investigate alteration in pain mechanisms. Methylphenidate infusions resulted in production of dysphorias similar to those occurring naturally but caused cardiac arrhythmias and have been discontinued.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02188-03 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Biological Studies of Borderline Personality Disorder

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D.L. Gardner	Staff Psychiatrist	NS, NIMH
Others:	R.W. Cowdry	Clinical Director	NIMH
	K. O'Leary	Social Worker (Research)	OD, DIRP, NIMH
	R.L. Post	Chief	BP, NIMH
	M. Kling	Medical Staff Fellow	BP, NIMH
	R. Coppola	Senior Engineer	LPP, NIMH
	D. Pickar	Chief, Sec on Clinical Studies	NS, NIMH
	P. Lucas	Clinical Fellow, NRSA Fellow	NS, NIMH

COOPERATING UNITS *(if any)*

Office of the Director, Division of Intramural Research Programs, NIMH; Biological Psychiatry Branch, NIMH; Laboratory of Psychology and Psychopathology, NIMH

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Clinical Studies

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.7	1.5	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.)*

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00117-11 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Alpha-Adrenergic and Prostaglandin Receptors in Human Blood Elements

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: M. S. Kafka Physiologist NS, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Molecular Pharmacology

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

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.)*

PROJECT HAS BEEN DISCONTINUED DUE TO PRINCIPAL INVESTIGATOR'S REASSIGNMENT TO THE OFFICE OF EXTRAMURAL PROJECT REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00117-11 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Alpha-Adrenergic and Prostaglandin Receptors in Human Blood Elements

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: M. S. Kafka Physiologist NS, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Molecular Pharmacology

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

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.)*

PROJECT HAS BEEN DISCONTINUED DUE TO PRINCIPAL INVESTIGATOR'S REASSIGNMENT TO THE OFFICE OF EXTRAMURAL PROJECT REVIEW

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00179-05 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Morphological Aspects of Peptides in Mammalian Brain

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	L. Skirboll	Sr. Staff Fellow	NS, NIMH
Others:	B. Robertson	Visiting Associate	NS, NIMH
	A. Kiss	Visiting Associate	NS, NIMH
	N. Harrison	Visiting Associate	LN, NINCDS

COOPERATING UNITS *(if any)*

Laboratory of Neurophysiology, NINCDS

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Unit on Electrophysiology, Section on Molecular Pharmacology

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

We have been developing several new anatomical methods to enhance our studies of coexisting transmitters in the brain. These include intensification of immunohistochemistry, double and triple labeling of single brain sections, new retrograde dyes such as fluorogold and in situ hybridization. In addition, we have been using these techniques to examine the effects of adrenalectomy on neuropeptide (dynorphin and vasopressin) in the hypothalamus and innervation of the phrenic motor nucleus. Finally, studies using antibodies specific to a subpopulation of dorsal root ganglion cells and studies tracing cholinergic projections to both substantia nigra and prefrontal cortex are underway.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00179-05 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

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PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	L. Skirboll	Sr. Staff Fellow	NS, NIMH
Others:	B. Robertson	Visiting Associate	NS, NIMH
	A. Kiss	Visiting Associate	NS, NIMH
	N. Harrison	Visiting Associate	LN, NINCDS

COOPERATING UNITS *(if any)*

Laboratory of Neurophysiology, NINCDS

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Unit on Electrophysiology, Section on Molecular Pharmacology

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

We have been developing several new anatomical methods to enhance our studies of coexisting transmitters in the brain. These include intensification of immunohistochemistry, double and triple labeling of single brain sections, new retrograde dyes such as fluorogold and in situ hybridization. In addition, we have been using these techniques to examine the effects of adrenalectomy on neuropeptide (dynorphin and vasopressin) in the hypothalamus and innervation of the phrenic motor nucleus. Finally, studies using antibodies specific to a subpopulation of dorsal root ganglion cells and studies tracing cholinergic projections to both substantia nigra and prefrontal cortex are underway.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02177-04 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Behavioral Functions of Neuropeptides

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J.N. Crawley	Senior Staff Fellow	NS, NIMH
Others:	L.R. Skirboll	Senior Staff Fellow	NS, NIMH
	D.W. Hommer	Staff Psychiatrist	NS, NIMH
	M.T. Kaltwasser	Guest Research	NS, NIMH
	J. Mastropaolo	Staff Fellow	NS, NIMH
	S.M. Paul	Chief	NS, NIMH
	D.M. Jacobowitz	Section Chief	LCS NIMH
	T. Moody	Associate Professor	GWU

COOPERATING UNITS *(if any)* Unit on Electrophysiology, Section on Molecular Pharmacology, NS and Section on Histopharmacology, Laboratory of Clinical Science, NIMH; George Washington University, Washington, DC; Maryland Psychiatric Institute, University of Maryland Medical School

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Molecular Pharmacology

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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 past decade has witnessed the discovery of forty or more peptides localized in neurons of mammalian brain. Many cases of peptides coexisting in the same neuron with classical transmitters have been described. Our laboratory is investigating the functional significance of coexisting peptides and transmitters in the central nervous system, using behavioral tools.

A) We previously showed that cholecystokinin (CCK) potentiates dopamine-induced hyperlocomotion in the nucleus accumbens, where CCK and dopamine coexist. This year, we began to investigate the functional significance of endogenous CCK. We developed a method to electrically stimulate the ventral tegmentum to increase locomotor behavior in a manner analogous to microinjection of DA into the nucleus accumbens. Preliminary data suggest that the CCK antagonist, proglumide, blocks hyperlocomotion induced by VTA stimulation, providing evidence for a functional role of endogenous CCK in the mesolimbic pathway.

B) Substance P (SP), corticotropin releasing factor (CRF) and acetylcholinesterase (Ach E) were found to coexist in dorsolateral tegmental neurons projecting to the rat prefrontal cortex. Substance P potentiated, while CRF inhibited, carbachol-induced "boxing". This year we found that substance P antagonists block carbachol-induced "boxing," providing evidence for a functional role of endogenous substance P in the medial prefrontal cortex.

C) Oxytocin and cholecystokinin coexist in the supraoptic and paraventricular nuclei of the hypothalamus. Cannulation of postsynaptic sites of this coexistence and evaluation of grooming behavior revealed a competitive interaction between microinjected CCK and OXY. This third case of coexistence, i.e., two peptides with no primary transmitter, appears to have a different mechanism of interaction from the cases outlined in A and B.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02177-04 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Behavioral Functions of Neuropeptides

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J.N. Crawley	Senior Staff Fellow	NS, NIMH
Others:	L.R. Skirboll	Senior Staff Fellow	NS, NIMH
	D.W. Hommer	Staff Psychiatrist	NS, NIMH
	M.T. Kaltwasser	Guest Research	NS, NIMH
	J. Mastropaolo	Staff Fellow	NS, NIMH
	S.M. Paul	Chief	NS, NIMH
	D.M. Jacobowitz	Section Chief	LCS NIMH
	T. Moody	Associate Professor	GWU

COOPERATING UNITS *(if any)* Unit on Electrophysiology, Section on Molecular Pharmacology, NS and Section on Histopharmacology, Laboratory of Clinical Science, NIMH; George Washington University, Washington, DC; Maryland Psychiatric Institute, University of Maryland Medical School

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Molecular Pharmacology

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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 past decade has witnessed the discovery of forty or more peptides localized in neurons of mammalian brain. Many cases of peptides coexisting in the same neuron with classical transmitters have been described. Our laboratory is investigating the functional significance of coexisting peptides and transmitters in the central nervous system, using behavioral tools.

A) We previously showed that cholecystokinin (CCK) potentiates dopamine-induced hyperlocomotion in the nucleus accumbens, where CCK and dopamine coexist. This year, we began to investigate the functional significance of endogenous CCK. We developed a method to electrically stimulate the ventral tegmentum to increase locomotor behavior in a manner analogous to microinjection of DA into the nucleus accumbens. Preliminary data suggest that the CCK antagonist, proglumide, blocks hyperlocomotion induced by VTA stimulation, providing evidence for a functional role of endogenous CCK in the mesolimbic pathway.

B) Substance P (SP), corticotropin releasing factor (CRF) and acetylcholinesterase (Ach E) were found to coexist in dorsolateral tegmental neurons projecting to the rat prefrontal cortex. Substance P potentiated, while CRF inhibited, carbachol-induced "boxing". This year we found that substance P antagonists block carbachol-induced "boxing," providing evidence for a functional role of endogenous substance P in the medial prefrontal cortex.

C) Oxytocin and cholecystokinin coexist in the supraoptic and paraventricular nuclei of the hypothalamus. Cannulation of postsynaptic sites of this coexistence and evaluation of grooming behavior revealed a competitive interaction between microinjected CCK and OXY. This third case of coexistence, i.e., two peptides with no primary transmitter, appears to have a different mechanism of interaction from the cases outlined in A and B.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02178-04 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Neuropharmacology of Anxiety

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J.N. Crawley	Senior Staff Fellow	NS, NIMH
	R.C. Drugan	NRSA Fellow	NS, NIHM
Others:	L.R. Skirboll	Senior Staff Fellow	NS, NIMH
	D.W. Hommer	Staff Psychiatrist	NS, NIMH
	M.D. Majewska	Visiting Associate	NS, NIMH
	J. Glowa	Senior Staff Fellow	NS, NIMH
	S.M. Paul	Chief	NS, NIMH
	P. Skolnick	Pharmacologist	LBC, NIADDK

COOPERATING UNITS *(if any)*

Unit on Electrophysiology, Section on Molecular Pharmacology, NS, NIMH; Laboratory on Bioorganic Chemistry, NIADDK.

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Molecular Pharmacology

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	1.5	

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

Animal models of anxiety are being used to investigate the biological mechanisms underlying anxiety-related behaviors. An endogenous mineralocorticoid metabolite of progesterone, THDOC, previously characterized for its high affinity for the central benzodiazepine receptor, was tested and found to have significant anxiolytic activity in both the mouse exploratory behavior model and the Vogel thirsty-lick conflict rat model for anxiety. In addition, the anxiety component of the learned helplessness model of depression was characterized in terms of benzodiazepine, GABA, and chloride channel binding, in Sprague-Dawley and Maudsley hyperactive rats.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02178-04 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Neuropharmacology of Anxiety

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J.N. Crawley	Senior Staff Fellow	NS, NIMH
	R.C. Drugan	NRSA Fellow	NS, NIHM
Others:	L.R. Skirboll	Senior Staff Fellow	NS, NIMH
	D.W. Hommer	Staff Psychiatrist	NS, NIMH
	M.D. Majewska	Visiting Associate	NS, NIMH
	J. Glowa	Senior Staff Fellow	NS, NIMH
	S.M. Paul	Chief	NS, NIMH
	P. Skolnick	Pharmacologist	LBC, NIADDK

COOPERATING UNITS *(if any)*

Unit on Electrophysiology, Section on Molecular Pharmacology, NS, NIMH; Laboratory on Bioorganic Chemistry, NIADDK.

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Molecular Pharmacology

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	1.5	

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

Animal models of anxiety are being used to investigate the biological mechanisms underlying anxiety-related behaviors. An endogenous mineralocorticoid metabolite of progesterone, THDOC, previously characterized for its high affinity for the central benzodiazepine receptor, was tested and found to have significant anxiolytic activity in both the mouse exploratory behavior model and the Vogel thirsty-lick conflict rat model for anxiety. In addition, the anxiety component of the learned helplessness model of depression was characterized in terms of benzodiazepine, GABA, and chloride channel binding, in Sprague-Dawley and Maudsley hyperactive rats.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02179-04 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Animal Models of Neuropsychiatric Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J.N. Crawley	Senior Staff Fellow	NS, NIMH
Others:	S.M. Paul	Chief	NS, NIMH
	I. Angel	Visiting Associate	NS, NIMH
	O.M. Wolkowitz	Medical Staff Fellow	NS, NIMH
	P. Suzdak	Staff Fellow	NS, NIMH
	D. Rubinow	Chief, Unit on Peptide Studies	BP, NIMH

COOPERATING UNITS *(if any)*

Section on Clinical Studies, NS and Biological Psychiatry Branch, NIMH

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Molecular Pharmacology

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

1) Our hamster separation model of depression was tested for changes in corticotropin releasing factor, ACTH and cortisol.
2) Mice treated chronically with steroids were tested for hyperactivity of their central dopamine pathways, both behaviorally and biochemically, as a model for steroid-induced psychoses.
3) The central hypothalamic binding site for anorectic drugs such as amphetamine was analyzed for its role in regulation of feeding behaviors.
4) A benzodiazepine which antagonizes the biochemical actions of ethanol in rat brain was found to prevent and reverse ethanol-induced intoxication in rats.
5) Behavioral analysis of rats treated chronically with interleukin-II revealed reductions in exploratory and social behaviors at doses of IL-II analogous to those which induce psychoses when used to treat cancer patients.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02179-04 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Animal Models of Neuropsychiatric Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	J.N. Crawley	Senior Staff Fellow	NS, NIMH
Others:	S.M. Paul	Chief	NS, NIMH
	I. Angel	Visiting Associate	NS, NIMH
	O.M. Wolkowitz	Medical Staff Fellow	NS, NIMH
	P. Suzdak	Staff Fellow	NS, NIMH
	D. Rubinow	Chief, Unit on Peptide Studies	BP, NIMH

COOPERATING UNITS *(if any)*

Section on Clinical Studies, NS and Biological Psychiatry Branch, NIMH

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Molecular Pharmacology

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

1) Our hamster separation model of depression was tested for changes in corticotropin releasing factor, ACTH and cortisol.
2) Mice treated chronically with steroids were tested for hyperactivity of their central dopamine pathways, both behaviorally and biochemically, as a model for steroid-induced psychoses.
3) The central hypothalamic binding site for anorectic drugs such as amphetamine was analyzed for its role in regulation of feeding behaviors.
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5) Behavioral analysis of rats treated chronically with interleukin-II revealed reductions in exploratory and social behaviors at doses of IL-II analogous to those which induce psychoses when used to treat cancer patients.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02180-04 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)* Electrophysiological Studies of Peptidergic and GABAergic Function in Mammalian Brain.

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D. Hommer	Staff Psychiatrist	NS, NIMH
Others:	L. Skirboll	Sr. Staff Fellow	NS, NIMH
	J.N. Crawley	Sr. Staff Fellow	NS, NIMH
	S.M. Paul	Chief	NS, NIMH
	B. Robertson	Guest Researcher	NS, NIMH
	G. Stoner	Guest Researcher	NS, NIMH
	M. Palkovits	Visiting Scientist	LCB,NIMH
	P. Clarke	Visiting Fellow	BP, NIMH

COOPERATING UNITS *(if any)*

Laboratory of Cell Biology, NIMH and Biological Psychiatry Branch, NIMH

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Unit on Electrophysiology, Section on Molecular Pharmacology

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

Using extracellular single unit recording techniques, we have examined the effects of stress and pharmacological agents which either alleviate or mimic the effects of stress on individual neurons in the rat substantia nigra (SN). Specifically, learned helplessness induced by uncontrollable stressful shocks results in a supersensitivity to gamma-amino butyric acid (GABA) agonists while shocks which are controllable do not produce GABAergic supersensitivity. The anxiogenic benzodiazepine (BZ) receptor ligand, beta-carboline carboxylate ethyl ester (βCCE) increases the activity of neurons in the SN zona reticulata (ZR) but had no effect on noradrenergic neurons in the locus coeruleus. Caffeine also mimics many of the effects of βCCE in the SN but its actions are not reversed by the specific BZ antagonist Ro15-1788 as are those of βCCE. Furthermore, the effects of caffeine could be blocked by lesions of the caudate nucleus while the effects of βCCE were unaffected by such lesions.

We have continued our studies on the interactions between endogenously occurring neuropeptides and classical neurotransmitters. All varieties of CCK-like peptides which bind to brain CCK receptors also potentiate DA in those areas where CCK and DA coexist while those CCK-like peptides which do not bind to this receptor are ineffectual in facilitating DA inhibition. The putative cholecystokinin (CCK) antagonists, proglumide and benzotript, were found to weakly block CCK in proportion to their potency at central CCK receptors.

Dynorphin (DYN) appears to modulate the response of SNZR neurons to GABA. Finally, we have examined the effects to cholinergic agents in the SN. Nicotinic agents appear to activate DA neurons in the SN through a central mechanism.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02180-04 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)* Electrophysiological Studies of Peptidergic and GABAergic Function in Mammalian Brain.

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D. Hommer	Staff Psychiatrist	NS, NIMH
Others:	L. Skirboll	Sr. Staff Fellow	NS, NIMH
	J.N. Crawley	Sr. Staff Fellow	NS, NIMH
	S.M. Paul	Chief	NS, NIMH
	B. Robertson	Guest Researcher	NS, NIMH
	G. Stoner	Guest Researcher	NS, NIMH
	M. Palkovits	Visiting Scientist	LCB,NIMH
	P. Clarke	Visiting Fellow	BP, NIMH

COOPERATING UNITS *(if any)*

Laboratory of Cell Biology, NIMH and Biological Psychiatry Branch, NIMH

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Unit on Electrophysiology, Section on Molecular Pharmacology

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

Using extracellular single unit recording techniques, we have examined the effects of stress and pharmacological agents which either alleviate or mimic the effects of stress on individual neurons in the rat substantia nigra (SN). Specifically, learned helplessness induced by uncontrollable stressful shocks results in a supersensitivity to gamma-amino butyric acid (GABA) agonists while shocks which are controllable do not produce GABAergic supersensitivity. The anxiogenic benzodiazepine (BZ) receptor ligand, beta-carboline carboxylate ethyl ester (βCCE) increases the activity of neurons in the SN zona reticulata (ZR) but had no effect on noradrenergic neurons in the locus coeruleus. Caffeine also mimics many of the effects of βCCE in the SN but its actions are not reversed by the specific BZ antagonist Ro15-1788 as are those of βCCE. Furthermore, the effects of caffeine could be blocked by lesions of the caudate nucleus while the effects of βCCE were unaffected by such lesions.

We have continued our studies on the interactions between endogenously occurring neuropeptides and classical neurotransmitters. All varieties of CCK-like peptides which bind to brain CCK receptors also potentiate DA in those areas where CCK and DA coexist while those CCK-like peptides which do not bind to this receptor are ineffectual in facilitating DA inhibition. The putative cholecystokinin (CCK) antagonists, proglumide and benzotript, were found to weakly block CCK in proportion to their potency at central CCK receptors.

Dynorphin (DYN) appears to modulate the response of SNZR neurons to GABA. Finally, we have examined the effects to cholinergic agents in the SN. Nicotinic agents appear to activate DA neurons in the SN through a central mechanism.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02182-04 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Toward the Visualization of Opiate Receptors in Living Humans

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	C. B. Pert	Pharmacologist	NS, NIMH
Others:	M. A. Channing	Physician	NM, CC
	R. D. Finn	Chief, Rad. Chem. Sec.	NM, CC
	S. M. Larson	Chief	NM, CC
	K. C. Rice	Pharmacologist	LC, NIADDK

COOPERATING UNITS *(if any)*

Nuclear Medicine, CC, and Laboratory of Chemistry, NIADDK

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Brain Biochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	1.5	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 distribution of positron emitting substances in brain can be followed by positron emission tomography (PET). We are developing ^{18}F-labeled high affinity opiate drugs to be injected into living humans for the visualization of opiate receptor patterns in vivo. It will be interesting to determine whether opiate receptor distribution patterns in cortex change as a function of attention and emotional states. Meanwhile, we have carefully documented the receptor-binding properties and kinetics of ^{3}H-cyclofoxy in rat brain after in vivo injection.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02182-04 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Toward the Visualization of Opiate Receptors in Living Humans

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	C. B. Pert	Pharmacologist	NS, NIMH
Others:	M. A. Channing	Physician	NM, CC
	R. D. Finn	Chief, Rad. Chem. Sec.	NM, CC
	S. M. Larson	Chief	NM, CC
	K. C. Rice	Pharmacologist	LC, NIADDK

COOPERATING UNITS *(if any)*

Nuclear Medicine, CC, and Laboratory of Chemistry, NIADDK

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Brain Biochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	1.5	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 distribution of positron emitting substances in brain can be followed by positron emission tomography (PET). We are developing ^{18}F-labeled high affinity opiate drugs to be injected into living humans for the visualization of opiate receptor patterns in vivo. It will be interesting to determine whether opiate receptor distribution patterns in cortex change as a function of attention and emotional states. Meanwhile, we have carefully documented the receptor-binding properties and kinetics of ^{3}H-cyclofoxy in rat brain after in vivo injection.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02183-04 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Is Schizophrenia an Autoimmune Neuropeptide Receptor Disease?

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	C. B. Pert	Pharmacologist	NS, NIMH
Others:	J. G. Knight	Guest Researcher	NS, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Brain Biochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	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 notion that schizophrenia has an important autoimmune component has been around for several decades, but has not previously been subjected to analysis by the most sensitive, modern techniques. We have hypothesized that early (perinatal) tolerance to viruses, which use the receptor molecule to gain cellular entry, causes this autoimmunity. We have developed a simple sensitive assay for detecting antibodies directed against human brain found in sera of schizophrenic patients and controls. We are now subjecting human brain membrane receptors to either native or denaturing solubilization conditions and separation by polyacrylamide gel electrophresis (PAGE). After visualization by antiserum or CSF from patients and controls, we hope to identify the specific brain antigens against which schizophrenics have generated antibodies.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02183-04 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

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Others:	J. G. Knight	Guest Researcher	NS, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Brain Biochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	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.)*

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02189-03 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Neuropeptides and their Receptors are Shared by the Brain and the Immune System

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	C. B. Pert	Pharmacologist	NS, NIMH
Others:	C. J. Wiedermann	Guest Researcher	NS, NIMH
	P. Sacerdote	Guest Researcher	NS, NIMH
	J. M. Hill	Senior Staff Fellow	NS, NIMH
	B. Zipser	Guest Researcher	NS, NIMH
	M. R. Ruff	Immunologist	LM, NIDR

COOPERATING UNITS *(if any)*

Cellular Immunology Section, Laboratory of Microbiology and Immunology, NIDR

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Brain Biochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

Neuropeptides, small signal peptides largely known for their role as transmitters of nerve impulses in the brain which mediate mood and emotion, have now been shown to regulate immune system function. Our work reveals that human monocytes have receptors and will respond chemotactically to numerous neuropeptides. Neuropeptides which we have reported on include β-endorphin and other opiates, substance P and bombesin. We have shown that a major class of psychoactive drugs, the benzodiazepines, are also potent chemoattractants. In this case we have directly demonstrated the presence of chemotactic receptors through ligand binding experiments. The presence of diverse, distinct neuropeptide chemotactic receptors on monocytes and other immune system cells suggests the existence of a neuroendocrine link between the brain and the immune system whose purpose is to integrate behavioral and emotional responses with immune system function.

In addition to the presence of neuropeptide receptors we have also been able to demonstrate that human alveolar macrophages store and secrete the neuropeptide bombesin. Neuropeptide synthesis is, therefore, a general feature of various immune cell populations. Such results are consistent with a multi-directional communication network via neuropeptides and their receptors. The purpose of this network is to link the body's cellular defense and repair systems with the nervous and endocrine systems and thereby integrate the internal millieu of the whole organism. The flow of information in this network is perceived by the human organisms emotional and/or altered states of consciousness. Ultimately, this results in behavioral decisions at the whole organism level. Additional work has suggested that a major cause of human cancer, small cell lung carcinoma, may not, as previously thought, arise from lung epithelium but originates from hemopoietic cells when the normal macrophage mediated repair of lung tissue is deranged by continuous heavy smoking.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02189-03 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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PI:	C. B. Pert	Pharmacologist	NS, NIMH
Others:	C. J. Wiedermann	Guest Researcher	NS, NIMH
	P. Sacerdote	Guest Researcher	NS, NIMH
	J. M. Hill	Senior Staff Fellow	NS, NIMH
	B. Zipser	Guest Researcher	NS, NIMH
	M. R. Ruff	Immunologist	LM, NIDR

COOPERATING UNITS *(if any)*

Cellular Immunology Section, Laboratory of Microbiology and Immunology, NIDR

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Brain Biochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

Neuropeptides, small signal peptides largely known for their role as transmitters of nerve impulses in the brain which mediate mood and emotion, have now been shown to regulate immune system function. Our work reveals that human monocytes have receptors and will respond chemotactically to numerous neuropeptides. Neuropeptides which we have reported on include β-endorphin and other opiates, substance P and bombesin. We have shown that a major class of psychoactive drugs, the benzodiazepines, are also potent chemoattractants. In this case we have directly demonstrated the presence of chemotactic receptors through ligand binding experiments. The presence of diverse, distinct neuropeptide chemotactic receptors on monocytes and other immune system cells suggests the existence of a neuroendocrine link between the brain and the immune system whose purpose is to integrate behavioral and emotional responses with immune system function.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02190-03 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Distribution and Properties of Opiate and Other Brain Receptors

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	C. B. Pert	Pharmacologist	NS, NIMH
Others:	B. Zipser	Guest Researcher	NS, NIMH
	J. B. O'Neill	Guest Researcher	NS, NIMH
	C. C. Smith	Chemist	NS, NIMH
	M. R. Ruff	Immunologist	LM, NIDR
	C. M. Fraser	Pharmacologist	LNP, NINCDS
	C. J. Venter	Chief, Recept. Biochem.	LNP, NINCDS

COOPERATING UNITS *(if any)*

Cellular Immunology Section, Laboratory of Microbiology and Immunology, NIDR, and Section on Receptor Biochemistry, Laboratory of Neurophysiology, NINCDS.

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Brain Biochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

Cross-linking is a relatively recent biochemical strategy for covalently affixing reversible ligands to their recognition molecules for subsequent electrophoretic analysis. [^{125}I]-Tyr^{27}-β-endorphin (prepared as originally described by Smythe and co-workers) binds stereospecifically to rat brain membranes. While some studies have suggested that the β-endorphin receptor is a unique "epsilon" opiate receptor, a larger body of evidence suggest that β-endorphin has high affinity for most if not all of the opiate receptors types and subtypes. Cross-linking opiate receptors from different tissue sources can potentially reveal much information about the molecular basis of apparent opiate receptor heterogeneity. Cross-linking, however, only fixes 1% of the bound trace and SDS-PAGE while exquisitely sensitive, can fail to reveal substantial inter-molecular differences. Cross-linking was performed with the homo bi-functional reagent Disuccinimidyl Suberate (DSS). The iodinated cross-linking products of Tetrahymena, leech CNS, and rat brain membranes (both type 1 and type 2 conditions) appeared indistinguishable on SDS-PAGE gel with major cross-linking products at 58K and 100-110K. The strong cross-linked bands produced by incubation in the presence of the inactive opiate ((+)-naloxone) was completely abolished by the same (10^{-6}M) concentration of its active isomer (-)-naloxone. Although we have thus far failed to distinguish between opiate receptors from a mammal, an invertebrate, and a unicellular organism, we continue to explore various conditions of binding, and electrophoresis, (e.g., reduced and unreduced) to examine possible receptor differences, both intra and inter species. Electrophoresis of proteolytic digests of cross-linked bands will be performed as a particularly sensitive method for distinguishing heterogeneity. Thus far, our cross-linking experiment suggest that the recognition molecule (the opiate receptor) which binds all opiate alkaloids and peptides is stable across evolution. As proposed, apparent physiological receptor heterogeneity is due to coupling to other membrane components.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

ZO1 MH 02190-03 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Distribution and Properties of Opiate and Other Brain Receptors

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	C. B. Pert	Pharmacologist	NS, NIMH
Others:	B. Zipser	Guest Researcher	NS, NIMH
	J. B. O'Neill	Guest Researcher	NS, NIMH
	C. C. Smith	Chemist	NS, NIMH
	M. R. Ruff	Immunologist	LM, NIDR
	C. M. Fraser	Pharmacologist	LNP, NINCDS
	C. J. Venter	Chief, Recept. Biochem.	LNP, NINCDS

COOPERATING UNITS *(if any)*

Cellular Immunology Section, Laboratory of Microbiology and Immunology, NIDR, and Section on Receptor Biochemistry, Laboratory of Neurophysiology, NINCDS.

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Brain Biochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

Cross-linking is a relatively recent biochemical strategy for covalently affixing reversible ligands to their recognition molecules for subsequent electrophoretic analysis. [^{125}I]-Tyr^{27}-β-endorphin (prepared as originally described by Smythe and co-workers) binds stereospecifically to rat brain membranes. While some studies have suggested that the β-endorphin receptor is a unique "epsilon" opiate receptor, a larger body of evidence suggest that β-endorphin has high affinity for most if not all of the opiate receptors types and subtypes. Cross-linking opiate receptors from different tissue sources can potentially reveal much information about the molecular basis of apparent opiate receptor heterogeneity. Cross-linking, however, only fixes 1% of the bound trace and SDS-PAGE while exquisitely sensitive, can fail to reveal substantial inter-molecular differences. Cross-linking was performed with the homo bi-functional reagent Disuccinimidyl Suberate (DSS). The iodinated cross-linking products of Tetrahymena, leech CNS, and rat brain membranes (both type 1 and type 2 conditions) appeared indistinguishable on SDS-PAGE gel with major cross-linking products at 58K and 100-110K. The strong cross-linked bands produced by incubation in the presence of the inactive opiate ((+)-naloxone) was completely abolished by the same (10^{-6}M) concentration of its active isomer (-)-naloxone. Although we have thus far failed to distinguish between opiate receptors from a mammal, an invertebrate, and a unicellular organism, we continue to explore various conditions of binding, and electrophoresis, (e.g., reduced and unreduced) to examine possible receptor differences, both intra and inter species. Electrophoresis of proteolytic digests of cross-linked bands will be performed as a particularly sensitive method for distinguishing heterogeneity. Thus far, our cross-linking experiment suggest that the recognition molecule (the opiate receptor) which binds all opiate alkaloids and peptides is stable across evolution. As proposed, apparent physiological receptor heterogeneity is due to coupling to other membrane components.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02191-01 NS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Brain Receptors for the AIDS Virus and Other Neurotrophic Viruses

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	C. B. Pert	Pharmacologist	NS, NIMH
Others:	J. M. Hill	Senior Staff Fellow	NS, NIMH
	R. M. Berman	Chemist	NS, NIMH
	M. R. Ruff	Immunologist	LM, NIDR
	W. L. Farrar	Senior Staff Fellow	LM, NCI
	F. W. Ruscetti	Section Chief	LM, NCI

COOPERATING UNITS *(if any)*

Cellular Immunology Section, Laboratory of Microbiology and Immunology, NIDR, and Laboratory of Molecular Immunoregulation, Biological Response Modifiers Program, Division of Cancer Treatment, NCI.

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Brain Biochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

We have demonstrated that the 60 kD protein previously characterized on a subset of T lymphocytes and named "T4", is another example of shared components between the brain and immune system. Thus, we have demonstrated that this cell surface molecule can be cross-linked to ^{125}I labeled AIDS virus envelope and immunoprecipitated by the Mab OKT4 in both T cells and brain. Furthermore, we have mapped the brain distribution pattern of the AIDS virus receptor, T4 in monkey, human and rat brain and shown that it is most enriched in areas of the cortex and the hippocampus which subserves cognition and other higher functions. Our work suggest that the neuropsychiatric effects of AIDS may not, as previously thought, be due to inflammatory processes but may be due to a direct neuronal infection of the virus.

We have idertified, synthesized, and studied an octapeptide "peptide T", which appears to be the critical attachment area of the AIDS viral envelope. Peptide T and several rationally designed peptide analogs appear to bind with high affinity to the AIDS virus receptor, blocking viral infectivity at very low concentrations. We expect that synthetic peptide heteropolymers employing this core pentapeptide attachment sequence will prove valuable as an approach for a vaccine for AIDS.

This method and approach appears useful for exploring the presence of other virus receptors in brain. For example, we have already observed that the Epstein-Barr virus which has been known to use the complement receptor on B cells as a receptor entry protein, may actually infect brain via the same receptor molecule which we have recently identified in brain.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

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PERIOD COVERED

October 1, 1985 to September 30, 1986

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

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	R. M. Berman	Chemist	NS, NIMH
	M. R. Ruff	Immunologist	LM, NIDR
	W. L. Farrar	Senior Staff Fellow	LM, NCI
	F. W. Ruscetti	Section Chief	LM, NCI

COOPERATING UNITS *(if any)*

Cellular Immunology Section, Laboratory of Microbiology and Immunology, NIDR, and Laboratory of Molecular Immunoregulation, Biological Response Modifiers Program, Division of Cancer Treatment, NCI.

LAB/BRANCH

Clinical Neuroscience Branch

SECTION

Section on Brain Biochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	

CHECK APPROPRIATE BOX(ES)

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☐ (a1) Minors

☐ (a2) Interviews

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

ZO1 MH 00153-09 CHP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Treatment of Obsessional Children and Adolescents with Clorimipramine

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Judith L. Rapoport, M.D., Chief, CHP, NIMH
David Shaffer, M.D., Columbia University
Martine Flament, M.D., Guest Researcher, CHP, NIMH
Dennis L. Murphy, M.D., Chief, LCS, NIMH
Theodore Zahn, Ph.D., Research Psychologist, LPP, NIMH
Agnes Whittaker, M.D., Columbia University
Paul Fedio, Ph.D., Acting Chief, CN, NINCDS
Martha Denckla, M.D., Chief, Autism & Behavioral Disorders Section, DNB, NINCDS

COOPERATING UNITS *(if any)*

Unit on Sleep Studies, CPB, NIMH; Laboratory of Psychology and Psychopathology, NIMH; Clinical Neuropharmacology Branch, NIMH; National Institute of Neurological and Communicative Disorders and Stroke; Columbia University

LAB/BRANCH

Child Psychiatry Branch

SECTION

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.50	1.75	.75

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.)*

Obsessive Compulsive Disorder has fascinated clinicians for hundreds of years, but because of the high proportion (30-40%) of cases with childhood onset, the disorder holds particular interest for child psychiatrists. Moreover, unlike depression and schizophrenia, the disorder appears in virtually identical form in children to that in adults.

New information derived from epidemiological, pharmacological and clinical descriptive studies, from studies of related disorders, and from a prospective study of 30 children with severe primary obsessive compulsive disorder, suggest that the disorder is considerably more common than had been thought and reaffirm intriguing neurological links, and severe morbidity of this condition if untreated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00153-09 CHP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

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PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

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David Shaffer, M.D., Columbia University
Martine Flament, M.D., Guest Researcher, CHP, NIMH
Dennis L. Murphy, M.D., Chief, LCS, NIMH
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Agnes Whittaker, M.D., Columbia University
Paul Fedio, Ph.D., Acting Chief, CN, NINCDS
Martha Denckla, M.D., Chief, Autism & Behavioral Disorders Section, DNB, NINCDS

COOPERATING UNITS *(if any)*

Unit on Sleep Studies, CPB, NIMH; Laboratory of Psychology and Psychopathology, NIMH; Clinical Neuropharmacology Branch, NIMH; National Institute of Neurological and Communicative Disorders and Stroke; Columbia University

LAB/BRANCH

Child Psychiatry Branch

SECTION

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.50	1.75	.75

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.)*

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00161-08 CHP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Behavioral Effects of Dietary Substances in Normal and Hyperactive Children

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Markus Kruesi, M.D., Senior Staff Fellow, CHP, NIMH
Martine Flament, M.D., Guest Researcher, CHP, NIMH
Marion Yarrow, Ph.D., LDP, NIMH
Carolyn Zahn-Waxler, M.D., LDP, NIMH
Thomas Uhde, M.D., BPB, NIMH

COOPERATING UNITS *(if any)*

Laboratory of Developmental Psychology, NIMH
Biological Psychiatry Branch, NIMH

LAB/BRANCH

Child Psychiatry Branch

SECTION

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.75	1.00	.75

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.)*

Seven-day consumption of sugar and other carbohydrates and challenge effects of glucose, sucrose (1.75gm/kg), aspartame (30mg/kg) and saccharin were compared for 32 male preschool aged children: 19 had histories of adverse behavioral response to sugar while 13 were familiar playmates with no such histories. There was no evidence of behavioral response to sugar on measures of activity, aggression, expression emotionality or anxiety. There was a slight but significant decrease in actometer rated motor activity following aspartame ingestion, the significance of which is unclear. No significant differences in dietary consumption of carbodrate or correlations between consumption and behavior were found.

The response of children with generalized anxiety disorder and of normal controls to caffeine (10 mg/kg) are being compared. To date, a total of four pairs have been examined with no evidence for greater responsivity of anxiety disordered children than controls. This is in contrast to studies with adult patients indicating caffeine hypersensitivity.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00161-08 CHP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Behavioral Effects of Dietary Substances in Normal and Hyperactive Children

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Markus Kruesi, M.D., Senior Staff Fellow, CHP, NIMH
Martine Flament, M.D., Guest Researcher, CHP, NIMH
Marion Yarrow, Ph.D., LDP, NIMH
Carolyn Zahn-Waxler, M.D., LDP, NIMH
Thomas Uhde, M.D., BPB, NIMH

COOPERATING UNITS *(if any)*

Laboratory of Developmental Psychology, NIMH
Biological Psychiatry Branch, NIMH

LAB/BRANCH

Child Psychiatry Branch

SECTION

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.75	1.00	.75

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.)*

Seven-day consumption of sugar and other carbohydrates and challenge effects of glucose, sucrose (1.75gm/kg), aspartame (30mg/kg) and saccharin were compared for 32 male preschool aged children: 19 had histories of adverse behavioral response to sugar while 13 were familiar playmates with no such histories. There was no evidence of behavioral response to sugar on measures of activity, aggression, expression emotionality or anxiety. There was a slight but significant decrease in actometer rated motor activity following aspartame ingestion, the significance of which is unclear. No significant differences in dietary consumption of carbodrate or correlations between consumption and behavior were found.

The response of children with generalized anxiety disorder and of normal controls to caffeine (10 mg/kg) are being compared. To date, a total of four pairs have been examined with no evidence for greater responsivity of anxiety disordered children than controls. This is in contrast to studies with adult patients indicating caffeine hypersensitivity.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00162-07 CHP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Treatment of Hyperactive Children with Desmethylimipramine

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Judith L. Rapoport, M.D., Chief, CHP, NIMH
Maureen Donnelly, M.D., Clinical Associate, CHP, NIMH
Alan Zametkin, M.D., Clinical Associate, CHP, NIMH
William Z. Potter, M.D., Ph.D., Chief, Section on Clinical Pharmacology, LCS, NIMH
Herbert Weingartner, Ph.D., Psychologist, LPP, NIMH
Markku Linnoila, M.D., Ph.D., Chief, LCS, NIAAA

COOPERATING UNITS *(if any)*

Laboratory of Psychology and Psychopathology, NIMH
Laboratory of Clinical Science, NIMH
Laboratory of Clinical Studies, NIAAA

LAB/BRANCH

Child Psychiatry Branch

SECTION

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.85	.60	.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.)*

Twenty-nine hyperactive boys were randomly assigned to treatment with desipramine (DMI) (n=17) or placebo (n=12) for 14 days in a non-crossover, double-blind study. There was immediate behavioral improvement at Day 3, sustained for two weeks; behavioral improvement did not correlate with plasma concentration of DMI, OH-DMI, or their sum at either Day 3 or 14.

There were no untoward side effects; there was a drug-induced increase in pulse and diastolic blood pressure. On drug, urinary excretion of NE, VMA, and MHPG was decreased at both Days 3 and 14. The decreases in both urinary and plasma MHPG showed significant correlations with behavioral improvement during the second week.

These data corroborate previous findings on sympathomimetic effects of tricyclics in children and support a nonadrenergic mechanism for mediation of drug effects on behavioral hyperactivity (Attention Deficit Disorder with Hyperactivity).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00162-07 CHP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

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PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Judith L. Rapoport, M.D., Chief, CHP, NIMH
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Alan Zametkin, M.D., Clinical Associate, CHP, NIMH
William Z. Potter, M.D., Ph.D., Chief, Section on Clinical Pharmacology, LCS, NIMH
Herbert Weingartner, Ph.D., Psychologist, LPP, NIMH
Markku Linnoila, M.D., Ph.D., Chief, LCS, NIAAA

COOPERATING UNITS *(if any)*

Laboratory of Psychology and Psychopathology, NIMH
Laboratory of Clinical Science, NIMH
Laboratory of Clinical Studies, NIAAA

LAB/BRANCH

Child Psychiatry Branch

SECTION

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.85	.60	.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.)*

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These data corrobate previous findings on sympathomimetic effects of tricyclics in children and support a nonadrenergic mechanism for mediation of drug effects on behavioral hyperactivity (Attention Deficit Disorder with Hyperactivity).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00177-05 CHP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Treatment of Hyperactive Children with Monoamine Oxidase Inhibitors

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Judith L. Rapoport, M.D., Chief, CHP, NIMH
Alan Zametkin, M. D., Clinical Associate, CHP, NIMH
Dennis Murphy, M.D., Chief, LCS, NIMH
Herbert Weingartner, Ph.D., Chief, Unit on Cognitive Studies, LPP, NIMH
Markku Linnoila, M.D., Ph.D., Chief, LCS, NIAAA
Farouk Karoum, Ph.D., NPB, NIMH
William Z. Potter, M.D., Ph.D., Chief, Section on Clinical Pharmacology, LCS, NIMH

COOPERATING UNITS *(if any)*

Laboratory of Clinical Science, NIMH; Laboratory of Clinical Studies, NIAAA
Neuropsychiatry Branch, NIMH
Laboratory of Psychology and Psychopathology, NIMH

LAB/BRANCH

Child Psychiatry Branch

SECTION

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

Forty-eight children with childhood Attention Deficit Disorder (ADD) have been treated with a selective or nonselective MAO inhibitor. The major findings to date are that both clorgyline, a selective MAO-A inhibitor, and tranylcyrpomine, a nonselective inhibitor, were effective in decreasing hyperactivity and improving attention, but that l-deprenyl, a selective MAO-B inhibitor, was not effective. There was a significant decrease in urinary MHPG excretion which showed some correlation with behavioral improvement both on clorgyline and tranylcypromine, and on d-amphetamine. However, this decrease in MHPG persisted for several weeks after drugs were stopped while there was immediate behavioral rebound off drug for both amphetamine and for the MAOIs.

Biochemical analysis of l-deprenyl subjects has not been completed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00177-05 CHP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

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PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Judith L. Rapoport, M.D., Chief, CHP, NIMH
Alan Zametkin, M. D., Clinical Associate, CHP, NIMH
Dennis Murphy, M.D., Chief, LCS, NIMH
Herbert Weingartner, Ph.D., Chief, Unit on Cognitive Studies, LPP, NIMH
Markku Linnoila, M.D., Ph.D., Chief, LCS, NIAAA
Farouk Karoum, Ph.D., NPB, NIMH
William Z. Potter, M.D., Ph.D., Chief, Section on Clinical Pharmacology, LCS, NIMH

COOPERATING UNITS *(if any)*

Laboratory of Clinical Science, NIMH; Laboratory of Clinical Studies, NIAAA
Neuropsychiatry Branch, NIMH
Laboratory of Psychology and Psychopathology, NIMH

LAB/BRANCH

Child Psychiatry Branch

SECTION

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

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Biochemical analysis of l-deprenyl subjects has not been completed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00178-05 CHP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Brain Structure and Function in Developmental Neuropsychiatric Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Judith M. Rumsey, Ph.D., Staff Fellow, CHP, NIMH
Connie Duncan, Ph.D., Staff Fellow, LPP, NIMH
Richard Coppola, Ph.D., LPP, NIMH
Stanley I. Rapoport, M.D., Chief, LN, NIA
Karen Berman, M.D., Staff Fellow, NPB, NIMH
Daniel Weinberger, M.D., Chief, NPB, NIMH
Martha B. Denckla, M.D., Chief, Autism & Behavioral Disorders Section, DNB, NINCDS
Michael Goldberg, M.D., LSR, NEI

COOPERATING UNITS *(if any)*

Laboratory of Psychology and Psychopathology, NIMH; Section on Autism,DNB,NINCDS; Section on Brain Aging and Dementia, NL, NIA; Section on Clinical Neuropsychiatry, NPB, NIMH; Laboratory of Sensorimotor Research, NEI

LAB/BRANCH

Child Psychiatry Branch

SECTION

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	1.05	1.50

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 first 15 right-handed men with severe developmental dyslexia and their matched controls have been studied with EEG spectral analysis, event-related potentials, xenon inhalation procedures for measuring regional cerebral blood flow, neurological examinations for soft signs, and neuropsychological testing. In addition, ten patients have been studied with magnetic resonance head scans in in pilot study. Subtle abnormalities of temporal symmetry are suggested by the preliminary finding that nine of ten patients show very symmetrical temporal lobe volumes, a finding compatible with neuropathological work on dyslexia. Cerebral blood flow data show group differences both in posterior (parietal) cortex and in frontal cortical regions. Event-related potential data suggest abnormalities in N100, N200, and P300 components, which differ qualitatively for dyslexic men with positive versus negative retrospective parent ratings for attention deficit disorder. Neuropsychological test data document continuing deficits in phonetic decoding and encoding, visual-verbal associative learning, verbal learning, and language processing in our adult dyslexic sample.

Dyslexic children with and without attention deficit disorder, math-disabled children, pure ADD children, and controls are being recruited for event-related potential studies, and eye movement studies. We are beginning a controlled, quantitative MRI study of our dyslexic adults and planning a PET-scan of this sample.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00178-05 CHP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

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Martha B. Denckla, M.D., Chief, Autism & Behavioral Disorders Section, DNB, NINCDS
Michael Goldberg, M.D., LSR, NEI

COOPERATING UNITS *(if any)*

Laboratory of Psychology and Psychopathology, NIMH; Section on Autism,DNB,NINCDS; Section on Brain Aging and Dementia, NL, NIA; Section on Clinical Neuropsychiatry, NPB, NIMH; Laboratory of Sensorimotor Research, NEI

LAB/BRANCH

Child Psychiatry Branch

SECTION

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	1.05	1.50

CHECK APPROPRIATE BOX(ES)

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

☒ (a1) Minors

☒ (a2) Interviews

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Dyslexic children with and without attention deficit disorder, math-disabled children, pure ADD children, and controls are being recruited for event-related potential studies, and eye movement studies. We are beginning a controlled, quantitative MRI study of our dyslexic adults and planning a PET-scan of this sample.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00301-04 CHP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Diagnosis in Child Psychiatry

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Judith L. Rapoport, M.D., Chief, CHP, NIMH
Maureen Donnelly, M.D., Clinical Associate, CHP, NIMH
Alan J. Zametkin, M.D., Staff Psychiatrist, CHP, NIMH
Mary Beth Ahearn, Ph.D., Psychologist, Johns Hopkins School of Mental Hygiene
Eric Taylor, M.D., Senior Registrar, The Maudsley Hospital, London, England
James Swanson, Ph.D., Professor of Psychology, University of California, Irvine, CA
Michael Rutter, M.D., Professor of Child Psychiatry, The Maudsley Hospital, London, England,

COOPERATING UNITS *(if any)*

Department of Psychiatry, Maudsley Hospital, London, England
Department of Pediatrics, University of California, Irvine, California

LAB/BRANCH

Child Psychiatry Branch

SECTION

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.80	.60	.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.)*

To investigate the basis for widely disparate rates in the diagnosis of childhood hyperactivity between the U.S. and U.K., research teams and clinician panels in both countries rated a set of 36 standardized case histories, using both ICD-9 and DSM-III diagnostic schemes. Half of the cases had brief videotaped interviews.

The rates for diagnosis of hyperactivity were affected by the diagnostic scheme, being considerably lower with ICD-9, which permits only one Axis I diagnosis. This effect was principally for British raters. With DSM-III, the rates were similar for British and American raters. Inter-rater agreement was acceptably high only for specialllly trained research teams: Within panels of experienced diagnosticians there was much disagreement. The presence of a videotape of part of the psychiatric interview did not affect inter-rater agreement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00301-04 CHP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Diagnosis in Child Psychiatry

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Judith L. Rapoport, M.D., Chief, CHP, NIMH
Maureen Donnelly, M.D., Clinical Associate, CHP, NIMH
Alan J. Zametkin, M.D., Staff Psychiatrist, CHP, NIMH
Mary Beth Ahearn, Ph.D., Psychologist, Johns Hopkins School of Mental Hygiene
Eric Taylor, M.D., Senior Registrar, The Maudsley Hospital, London, England
James Swanson, Ph.D., Professor of Psychology, University of California, Irvine, CA
Michael Rutter, M.D., Professor of Child Psychiatry, The Maudsley Hospital, London, England,

COOPERATING UNITS *(if any)*

Department of Psychiatry, Maudsley Hospital, London, England
Department of Pediatrics, University of California, Irvine, California

LAB/BRANCH

Child Psychiatry Branch

SECTION

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.80	.60	.20

CHECK APPROPRIATE BOX(ES)

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

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02240-02 CHP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Neurobiology of Attention Deficit Disorder

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Judith L. Rapoport, M.D., Chief, CHP, NIMH
Alan J. Zametkin, M.D., Staff Psychiatrist, CHP, NIMH
Markus J.P. Kruesi, M.D., CHP, NIMH
William Z. Potter, M.D., Ph.D., Chief, Section on Clinical Pharmacology, LCS, NIMH
Markku Linnoila, M.D., Ph.D., Chief, LCS, NIAAA
Robert M. Cohen, M.D., Ph.D., Chief, Section on Clinical Brain Imaging, LCM, NIMH

COOPERATING UNITS *(if any)*

Section on Clinical Pharmacology, LCS, NIMH
National Institute on Alcohol Abuse and Alcoholism
Section on Clinical Brain Imaging, LCM, NIMH

LAB/BRANCH

Child Psychiatry Branch

SECTION

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.00	.50	.50

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 pathophysiology of Attention Deficit Disorder with Hyperactivity (ADDH), and to develop new treatments, a therapeutic trial of the amino acid, d-phenylalanine, was completed over the past nine months. Eleven ADDH boys participated in a placebo controlled double-blind evaluation of phenylalanine (20/mg/kg/day) and placebo. Phenylalanine had no significant effect upon behavior in spite of elevated blood phenylalanine levels (up to 120 un/l).

In an attempt to localize abnormal patterns of cerebral glucose metabolism and cerebral flow in adults with Attention Deficit Disorder (ADD) Residual Type, parents of diagnosed hyperactive children are being studied using the 2-deoxyfluoroglucose method of Positron Emission Tomography (PET). To date, 18 patients have been scanned; preliminary results showed decreased cortisol glucose utilization. Eleven parents were rescanned after receiving dextroamphetamine; results are being analyzed.

Because of reports that the spinal fluid (CSF) 5HIAA, a serotonin metabolite; may be low in severely impulsive or aggressive adults, a study has been initiated to compare spinal fluid catecholamine and indoleamine metabolites in severely aggressive, conduct disordered children with and without ADD to children with other neurological problems. Peripheral measures of catecholamines will also be obtained.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02240-02 CHP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Neurobiology of Attention Deficit Disorder

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Judith L. Rapoport, M.D., Chief, CHP, NIMH
Alan J. Zametkin, M.D., Staff Psychiatrist, CHP, NIMH
Markus J.P. Kruesi, M.D., CHP, NIMH
William Z. Potter, M.D., Ph.D., Chief, Section on Clinical Pharmacology, LCS, NIMH
Markku Linnoila, M.D., Ph.D., Chief, LCS, NIAAA
Robert M. Cohen, M.D., Ph.D., Chief, Section on Clinical Brain Imaging, LCM, NIMH

COOPERATING UNITS *(if any)*

Section on Clinical Pharmacology, LCS, NIMH
National Institute on Alcohol Abuse and Alcoholism
Section on Clinical Brain Imaging, LCM, NIMH

LAB/BRANCH

Child Psychiatry Branch

SECTION

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.00	.50	.50

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 pathophysiology of Attention Deficit Disorder with Hyperactivity (ADDH), and to develop new treatments, a therapeutic trial of the amino acid, d-phenylalanine, was completed over the past nine months. Eleven ADDH boys participated in a placebo controlled double-blind evaluation of phenylalanine (20/mg/kg/day) and placebo. Phenylalanine had no significant effect upon behavior in spite of elevated blood phenylalanine levels (up to 120 un/l).

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Because of reports that the spinal fluid (CSF) 5HIAA, a serotonin metabolite; may be low in severely impulsive or aggressive adults, a study has been initiated to compare spinal fluid catecholamine and indoleamine metabolites in severely aggressive, conduct disordered children with and without ADD to children with other neurological problems. Peripheral measures of catecholamines will also be obtained.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00274-12 LCS

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Methods of Ionization in Mass Spectrometry

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Sanford P. Markey, Chief, Section on Analytical Biochemistry, LCS, NIMH

COOPERATING UNITS *(if any)*

Biomedical Engineering and Instrumentation Branch, DRS
Department of Pharmacology, George Washington University, Washington, DC

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Analytical Biochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.7	.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.)*

The dual cell Fourier transform mass spectrometer has been tested in various modes of sample introduction and found to have several basic design flaws precluding its usage as a routine analytical instrument. Experiments using electron ionization - probe analysis, laser desorption, and gas chromatography have served to suggest alternative hardware and software designs which are presently being built and which will be installed in the next year. The instrument has been used to characterize synthetic intermediates and products, particularly in a high resolution mode.

Collaborative studies on element and nuclide selective analyses using a microwave reaction interface to combust organic compounds and analyze the resulting species are continuing.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00274-12 LCS

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Methods of Ionization in Mass Spectrometry

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Sanford P. Markey, Chief, Section on Analytical Biochemistry, LCS, NIMH

COOPERATING UNITS *(if any)*

Biomedical Engineering and Instrumentation Branch, DRS
Department of Pharmacology, George Washington University, Washington, DC

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Analytical Biochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.7	.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.)*

The dual cell Fourier transform mass spectrometer has been tested in various modes of sample introduction and found to have several basic design flaws precluding its usage as a routine analytical instrument. Experiments using electron ionization - probe analysis, laser desorption, and gas chromatography have served to suggest alternative hardware and software designs which are presently being built and which will be installed in the next year. The instrument has been used to characterize synthetic intermediates and products, particularly in a high resolution mode.

Collaborative studies on element and nuclide selective analyses using a microwave reaction interface to combust organic compounds and analyze the resulting species are continuing.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00276-07 LCS

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Metabolism of Melatonin

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Sanford P. Markey, Chief, Section on Analytical Biochemistry, LCS, NIMH

COOPERATING UNITS *(if any)*

Section on Neuroendocrinology, LDN, NICHD
Office of the Chief, LCS, NIMH
Department of Pediatrics, USUHS
Clin. Psychobiol. Branch, NIMH

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Analytical Biochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	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 major urinary metabolite of the pineal hormone melatonin, 6-hydroxy-melatonin is being quantified by a gas chromatographic-mass spectrometric method. Urinary excretion rates of this metabolite are being used to determine the possible role of the pineal gland in human biology. Collaborative studies on the effect of various drugs on melatonin secretion are in progress - tricyclic antidepresssants, monoamine oxidase inhibitors, and a serotonin reuptake blocker. Other collaborative studies include an effort to measure melatonin changes during the seasonal estrus cycle in monkeys; demonstration of the neural pathway ennervating the pineal gland in rats; and the correlation between plasma melatonin, cerebrospinal fluid melatonin and urinary 6-hydroxy-melatonin in humans.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00276-07 LCS

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Metabolism of Melatonin

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Sanford P. Markey, Chief, Section on Analytical Biochemistry, LCS, NIMH

COOPERATING UNITS *(if any)*

Section on Neuroendocrinology, LDN, NICHD
Office of the Chief, LCS, NIMH
Department of Pediatrics, USUHS
Clin. Psychobiol. Branch, NIMH

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Analytical Biochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	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 major urinary metabolite of the pineal hormone melatonin, 6-hydroxy-melatonin is being quantified by a gas chromatographic-mass spectrometric method. Urinary excretion rates of this metabolite are being used to determine the possible role of the pineal gland in human biology. Collaborative studies on the effect of various drugs on melatonin secretion are in progress - tricyclic antidepressants, monoamine oxidase inhibitors, and a serotonin reuptake blocker. Other collaborative studies include an effort to measure melatonin changes during the seasonal estrus cycle in monkeys; demonstration of the neural pathway ennervating the pineal gland in rats; and the correlation between plasma melatonin, cerebrospinal fluid melatonin and urinary 6-hydroxy-melatonin in humans.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00277-07 LCS

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Synthesis of Stable Isotope-Labeled Compounds

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Sanford P. Markey, Chief, Section on Analytical Biochemistry, LCS, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Analytical Biochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS	PROFESSIONAL:	OTHER:
1.2	1.2	0

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

Stable and some radioisotope labeled compounds have been synthesized to support other laboratory projects. Structural analogues of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine were prepared, as well as $^{14}C_6$(phenyl)-MPTP. The synthesis and purification of $^{13}C_6$(phenyl)-norepinephrine from guaiacol has been completed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00277-07 LCS

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Synthesis of Stable Isotope-Labeled Compounds

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Sanford P. Markey, Chief, Section on Analytical Biochemistry, LCS, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Analytical Biochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	1.2	0

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

Stable and some radioisotope labeled compounds have been synthesized to support other laboratory projects. Structural analogues of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine were prepared, as well as $^{14}C_6$(phenyl)-MPTP. The synthesis and purification of $^{13}C_6$(phenyl)-norepinephrine from guaiacol has been completed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 00279-04 LCS

PERIOD COVERED: October 1, 1985 through September 30, 1986

TITLE OF PROJECT (40 characters or less. Title must fit on one line between the borders.): Pharmacology of Neurotoxins

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Sanford P. Markey, Chief, Section on Analytical Biochemistry

COOPERATING UNITS (if any)
Laboratory of Neurophysiology, NIMH
Office of the Director, IRP, NINCDS

LAB/BRANCH: Laboratory of Clinical Science

SECTION: Analytical Biochemistry

INSTITUTE AND LOCATION: NIMH, ADAMHA, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.4	2.0	2.4

CHECK APPROPRIATE BOX(ES):

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

☐ (a1) Minors

☐ (a2) Interviews

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

The mechanism of action and the metabolism of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is being studied in several animal species. $^{14}C_6$-MPTP has been prepared and is being used to characterize metabolic differences between effected and resistant animal species. In mouse brain, identified metabolites include 4-phenyl-1,2,3,6-tetrahydropyridine (PTP) and 1-methyl-4-phenyl-2-pyridone.

Rabbit antibodies to MPTP and MPP^+ have been raised using bovine serum albumin diazolinked to 3'- and 4'-amino MPTP and MPP^+ analogues as antigens. No differences in specificity of the antibodies was found with regard to the 3'- or 4'-linkage. An enzyme-linked immunoassay procedure has been devised using a second antigen, and commercial horseradish peroxidase linked to goat-antirabbit antibody. Anti-MPTP antibodies detected MPTP in mouse brain extracts derived from as little as 5 µg of tissue. The hypothesis that Parkinson's disease is caused by a neurotoxin structurally related to MPTP will be tested with these antibodies and extracts from brains of patients with Parkinson's disease.

Structure activity relationships of MPTP analogs have been tested in mice and dogs. Of the three amine substituted analogs (2'-, 3'-, and 4'-amino MPTP), the 4'-NH_2 MPTP caused some depletion of striatal dopamine in the mouse, but no cell loss. In the dog, a dose three times that required for MPTP causes loss of dopamine and cell death in the substantia nigra. Because the 4'-NH_2 MPTP does not appear to be metabolized in the same way as MPTP, new insights into the mechanism of action of these dopaminergic neurotoxins should result.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00279-04 LCS

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Pharmacology of Neurotoxins

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Sanford P. Markey, Chief, Section on Analytical Biochemistry

COOPERATING UNITS (if any)

Laboratory of Neurophysiology, NIMH
Office of the Director, IRP, NINCDS

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Analytical Biochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.4	2.0	2.4

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

The mechanism of action and the metabolism of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) is being studied in several animal species. $^{14}C_6$-MPTP has been prepared and is being used to characterize metabolic differences between effected and resistant animal species. In mouse brain, identified metabolites include 4-phenyl-1,2,3,6-tetrahydropyridine (PTP) and 1-methyl-4-phenyl-2-pyridone.

Rabbit antibodies to MPTP and MPP^+ have been raised using bovine serum albumin diazolinked to 3'- and 4'-amino MPTP and MPP^+ analogues as antigens. No differences in specificity of the antibodies was found with regard to the 3'- or 4'-linkage. An enzyme-linked immunoassay procedure has been devised using a second antigen, and commercial horseradish peroxidase linked to goat-antirabbit antibody. Anti-MPTP antibodies detected MPTP in mouse brain extracts derived from as little as 5 µg of tissue. The hypothesis that Parkinson's disease is caused by a neurotoxin structurally related to MPTP will be tested with these antibodies and extracts from brains of patients with Parkinson's disease.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02241-02 LCS

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Positron Emission Tomographic Imaging of Neurotransmitters and Their Turnover

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

C.C. Chiueh	Special Expert	LCS	NINCDS

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Analytical Biochemistry

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	0.8	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.)*

Work from this project is incorporated into project Z01 MH 02296 LCM.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02241-02 LCS

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Positron Emission Tomographic Imaging of Neurotransmitters and Their Turnover

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

C.C. Chiueh	Special Expert	LCS	NINCDS

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Analytical Biochemistry

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	0.8	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.)*

Work from this project is incorporated into project Z01 MH 02296 LCM.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00351-12-LCS

PERIOD COVERED

October 1, 1985 - September 30, 1986

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

Clinical Pharmacology of the Central Nervous System

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

David C. Jimerson, M.D., Chief, Section on Biomedical Psychiatry

COOPERATING UNITS *(if any)*

SAB, LCS, NIMH; SCS, NSB, NIMH

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Biomedical Psychiatry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	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.)*

During this year studies on catecholamine metabolism focused on collaborative investigations evaluating the relationship between norepinephrine turnover and activity of the hypothalamic-pituitary-adrenal axis in depression. These studies extended previous work by our group showing elevated catecholamine turnover in hypercortisolemic depressed patients. In preclinical studies, we began a series of investigations to evaluate the effects of altered feeding patterns, stress, and pharmacologic treatments on the regulation of appetitive behavior, satiety responses and body weight, with particular focus on the influence of central monoamine and endogenous opiate systems. Preliminary studies in rodents showed that naloxone produced dose-dependent attenuation of sham feeding of sucrose solutions following 18 hr. food deprivation. The influence of varying deprivation schedules on this opiate effect is under current investigation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 00351-12-LCS

PERIOD COVERED
October 1, 1985 - September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Clinical Pharmacology of the Central Nervous System

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
David C. Jimerson, M.D., Chief, Section on Biomedical Psychiatry

COOPERATING UNITS *(if any)*
SAB, LCS, NIMH; SCS, NSB, NIMH

LAB/BRANCH
Laboratory of Clinical Science

SECTION
Section on Biomedical Psychiatry

INSTITUTE AND LOCATION
NIMH, ADAMHA, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	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.)*

During this year studies on catecholamine metabolism focused on collaborative investigations evaluating the relationship between norepinephrine turnover and activity of the hypothalamic-pituitary-adrenal axis in depression. These studies extended previous work by our group showing elevated catecholamine turnover in hypercortisolemic depressed patients. In preclinical studies, we began a series of investigations to evaluate the effects of altered feeding patterns, stress, and pharmacologic treatments on the regulation of appetitive behavior, satiety responses and body weight, with particular focus on the influence of central monoamine and endogenous opiate systems. Preliminary studies in rodents showed that naloxone produced dose-dependent attenuation of sham feeding of sucrose solutions following 18 hr. food deprivation. The influence of varying deprivation schedules on this opiate effect is under current investigation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02289-02-LCS

PERIOD COVERED
October 1, 1985 - September 30, 1986

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

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

David C. Jimerson, M.D., Chief, Section on Biomedical Psychiatry

COOPERATING UNITS *(if any)*
SCN, LCS, NIMH; SCP, LCS, NIMH; SCN, BPB, NIMH; CNG, NIMH; SCS, NSB, NIMH

LAB/BRANCH
Laboratory of Clinical Science

SECTION
Section on Biomedical Psychiatry

INSTITUTE AND LOCATION
NIMH, ADAMHA, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.7	2.7	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.)*

Research on the syndromes of bulimia and anorexia nervosa during the past year included neurotransmitter, neuropeptide, neuroendocrine, metabolic, pharmacologic and related behavioral studies on neurobiologic factors thought to contribute to the etiology of these disorders, and to their variable responsiveness to available treatments. Consistent with preclinical data implicating hypothalamic serotonin dysregulation in impaired post-prandial satiety, preliminary pharmacological challenge studies with the serotonin agonist m-chlorophenylpiperazine (m-CPP) demonstrated blunted plasma prolactin responses in bulimic patients. Administration of m-CPP also resulted in migraine-like headaches in a high percentage of bulimic patients with a personal and family history of migraine headache. Follow-up studies of norepinephrine activity in eating disorder patients demonstrated that norepinephrine concentrations were low in both cerebrospinal fluid and plasma of binge abstinent normal weight bulimic patients. Studies on body weight regulation and energy metabolism documented a pattern of relatively low daily caloric intake in weight stable bulimic patients, suggesting increased efficiency of energy utilization. Conversely, substantial increases in metabolic activity (measured by indirect calorimetry) were measured in anorexic patients during weight gain, explaining in part the high caloric requirements for weight restoration in these patients. Collaborative studies utilizing the opiate antagonist naloxone and a glucocorticoid antagonist were initiated to follow up on our previous findings of dysregulation of opiate and hypothalamic-pituitary-adrenal function in anorexic patients. Initial interviews were begun for a family study of affective illness and other psychiatric disorders in relatives of patients with bulimic disorder.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02289-02-LCS

PERIOD COVERED

October 1, 1985 - September 30, 1986

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

Psychobiology of Eating Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

David C. Jimerson, M.D., Chief, Section on Biomedical Psychiatry

COOPERATING UNITS *(if any)*

SCN, LCS, NIMH; SCP, LCS, NIMH; SCN, BPB, NIMH; CNG, NIMH; SCS, NSB, NIMH

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Biomedical Psychiatry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.7	2.7	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.)*

Research on the syndromes of bulimia and anorexia nervosa during the past year included neurotransmitter, neuropeptide, neuroendocrine, metabolic, pharmacologic and related behavioral studies on neurobiologic factors thought to contribute to the etiology of these disorders, and to their variable responsiveness to available treatments. Consistent with preclinical data implicating hypothalamic serotonin dysregulation in impaired post-prandial satiety, preliminary pharmacological challenge studies with the serotonin agonist m-chlorophenylpiperazine (m-CPP) demonstrated blunted plasma prolactin responses in bulimic patients. Administration of m-CPP also resulted in migraine-like headaches in a high percentage of bulimic patients with a personal and family history of migraine headache. Follow-up studies of norepinephrine activity in eating disorder patients demonstrated that norepinephrine concentrations were low in both cerebrospinal fluid and plasma of binge abstinent normal weight bulimic patients. Studies on body weight regulation and energy metabolism documented a pattern of relatively low daily caloric intake in weight stable bulimic patients, suggesting increased efficiency of energy utilization. Conversely, substantial increases in metabolic activity (measured by indirect calorimetry) were measured in anorexic patients during weight gain, explaining in part the high caloric requirements for weight restoration in these patients. Collaborative studies utilizing the opiate antagonist naloxone and a glucocorticoid antagonist were initiated to follow up on our previous findings of dysregulation of opiate and hypothalamic-pituitary-adrenal [illegible] in anorexic patients. Initial interviews were begun for a family study of affective illness and other psychiatric disorders in relatives of patients with bulimic disorder.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 00326-13 LCS

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Clinical Neuropharmacology and Psychobiology of Depression and Mania

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dennis L. Murphy, M.D., Chief
Section on Clinical Neuropharmacology, LCS, NIMH

COOPERATING UNITS *(if any)*

BP, CPB, LCS, NIMH; HEB, NHLBI; VA Medical Center, Bronx, NY; Upstate Medical Center, SUNY; Maudsley Institute, London

LAB/BRANCH
Laboratory of Clinical Science

SECTION
Section on Clinical Neuropharmacology

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS: 3.1	PROFESSIONAL: 2.0	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.)*

In studies exploring the net physiological consequences of antidepressant drug treatment, the selective monoamine oxidase (MAO) type A inhibitor clorgyline and the non-selective inhibitor tranylcypromine were both found to increase early morning plasma melatonin concentrations in depressed patients, while the clinically less effective inhibitor of MAO-B, deprenyl, did not affect melatonin. In related animal studies, clorgyline had marked effects in reducing the firing rates of neurons in the locus coeruleus of rodents after both single, high dose clorgyline administration as well as after chronic treatment. Like other effects of clorgyline on β-adrenoceptors and cyclic AMP changes, this drug altered dopamine function (as reflected in apomorphine-induced stereotypy) only after chronic administration. In rhesus monkeys, a number of newer reversible MAO-A inhibitors had lesser effects on neuroamines and amine receptor functions than had been found with clorgyline and other clinically effective MAO-inhibitors, raising questions about their future utility as antidepressant agents, despite their more favorable side effect profile.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00326-13 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Clinical Neuropharmacology and Psychobiology of Depression and Mania

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dennis L. Murphy, M.D., Chief
Section on Clinical Neuropharmacology, LCS, NIMH

COOPERATING UNITS *(if any)*

BP, CPB, LCS, NIMH; HEB, NHLBI; VA Medical Center, Bronx, NY; Upstate Medical Center, SUNY; Maudsley Institute, London

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Clinical Neuropharmacology

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS: 3.1	PROFESSIONAL: 2.0	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.)*

In studies exploring the net physiological consequences of antidepressant drug treatment, the selective monoamine oxidase (MAO) type A inhibitor clorgyline and the non-selective inhibitor tranylcypromine were both found to increase early morning plasma melatonin concentrations in depressed patients, while the clinically less effective inhibitor of MAO-B, deprenyl, did not affect melatonin. In related animal studies, clorgyline had marked effects in reducing the firing rates of neurons in the locus coeruleus of rodents after both single, high dose clorgyline administration as well as after chronic treatment. Like other effects of clorgyline on β-adrenoceptors and cyclic AMP changes, this drug altered dopamine function (as reflected in apomorphine-induced stereotypy) only after chronic administration. In rhesus monkeys, a number of newer reversible MAO-A inhibitors had lesser effects on neuroamines and amine receptor functions than had been found with clorgyline and other clinically effective MAO-inhibitors, raising questions about their future utility as antidepressant agents, despite their more favorable side effect profile.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00332-08

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Animal Models for the Study of Neuropharmacologic Effects

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Charanjit S. Aulakh Staff Fellow, LCS, NIMH

COOPERATING UNITS *(if any)*

LCM, NIMH

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Clinical Neuropharmacology

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.3	0.8	0.5

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

Administration of the 5-HT_{1B} receptor agonist m-chlorophenyl-piperazine (m-CPP) to rats produced dose-dependent decreases in the locomotor activity and food intake. The locomotor suppressant effect of m-CPP was inhibited by the serotonergic antagonist, metergoline, but not by phentolamine, propranolol, clonidine, or haloperidol. The locomotor and the food-intake suppressant effects of m-CPP were enhanced following long-term treatment with the tricyclic antidepressant imipramine. These findings are compatible with the development of functional super-sensitivity of 5-HT_{1B} receptors during long-term antidepressant drug treatment. In another study, the food-intake suppressant effect of m-CPP was potentiated following short-term lithium treatment, while long-term lithium treatment caused attenuation, thus suggesting development of functional subsensitivity of 5-HT_{1B} receptors following long-term lithium treatment. The combination of these results indicates that various agents effective in different types of affective disorders exert a modulatory influenceon serotonergic function in vivo. These results in animal model studies also help validate the use of m-CPP as an index of central serotonergic function in investigations in humans.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00332-08

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Animal Models for the Study of Neuropharmacologic Effects

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Charanjit S. Aulakh Staff Fellow, LCS, NIMH

COOPERATING UNITS *(if any)*

LCM, NIMH

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Clinical Neuropharmacology

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.3	0.8	0.5

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

Administration of the 5-HT_{1B} receptor agonist m-chlorophenyl-piperazine (m-CPP) to rats produced dose-dependent decreases in the locomotor activity and food intake. The locomotor suppressant effect of m-CPP was inhibited by the serotonergic antagonist, metergoline, but not by phentolamine, propranolol, clonidine, or haloperidol. The locomotor and the food-intake suppressant effects of m-CPP were enhanced following long-term treatment with the tricyclic antidepressant imipramine. These findings are compatible with the development of functional super-sensitivity of 5-HT_{1B} receptors during long-term antidepressant drug treatment. In another study, the food-intake suppressant effect of m-CPP was potentiated following short-term lithium treatment, while long-term lithium treatment caused attenuation, thus suggesting development of functional subsensitivity of 5-HT_{1B} receptors following long-term lithium treatment. The combination of these results indicates that various agents effective in different types of affective disorders exert a modulatory influenceon serotonergic function in vivo. These results in animal model studies also help validate the use of m-CPP as an index of central serotonergic function in investigations in humans.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00336-07 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

The Phenomenology and Treatment of Obsessive-Compulsive Disorder in Adults

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	T. R. Insel	Staff Physician	LCS, NIMH
Others:	D. L. Murphy	Chief	LCS, NIMH
	J. Zohar	Staff Physician	LCS, NIMH
	E. A. Mueller	Staff Physician	LCS, NIMH
	R. Zohar-Kadouch	Guest Worker	LCS, NIMH

COOPERATING UNITS *(if any)*

Neuropsychiatry Branch, NIMH, Laboratory of Cerebral Metabolism, NIMH

LAB/BRANCH

Laboratory of Clinical Science, NIMH

SECTION

Section on Comparative Studies of Brain and Behavior

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	0.7	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.)*

Obsessive-compulsive disorder has been studied from several different perspectives since the beginning of this project in 1980. A major focus in this past year has been the continued investigation of an abnormality in serotonergic function in this syndrome. Previously we showed that the tricyclic antidepressant clomipramine was specifically anti-obsessional, in contrast to several other antidepressants. As clomipramine is considerably more potent than other tricyclic antidepressants in its serotonergic effects, we hypothesized that drugs with selective actions on serotonin receptors would affect obsessional symptoms. Indeed, administration of the selective serotonin postsynaptic receptor agonist m-chlorophenylpiperazine (m-CPP) appeared to increase obsessional symptoms and anxiety in patients with obsessive-compulsive disorder but not in healthy controls. By contrast, the post-synaptic serotonin receptor antagonist, metergoline was associated with a slight decrease in obsessional symptoms. The obsession-inducing effects of m-CPP appear to be blocked by chronic clomipramine administration.

Continued studies of cerebral blood flow in obsessive-compulsive patients have revealed an increase in cortical flow during "imaginal flooding" and a profound decrease in cortical flow during actual exposure to the obsessional stimulus.

Finally, we continue to track the natural course of this disorder with follow-up studies of patients treated between 1980-1983.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00336-07 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

The Phenomenology and Treatment of Obsessive-Compulsive Disorder in Adults

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	T. R. Insel	Staff Physician	LCS, NIMH
Others:	D. L. Murphy	Chief	LCS, NIMH
	J. Zohar	Staff Physician	LCS, NIMH
	E. A. Mueller	Staff Physician	LCS, NIMH
	R. Zohar-Kadouch	Guest Worker	LCS, NIMH

COOPERATING UNITS *(if any)*

Neuropsychiatry Branch, NIMH, Laboratory of Cerebral Metabolism, NIMH

LAB/BRANCH

Laboratory of Clinical Science, NIMH

SECTION

Section on Comparative Studies of Brain and Behavior

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	0.7	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.)*

Obsessive-compulsive disorder has been studied from several different perspectives since the beginning of this project in 1980. A major focus in this past year has been the continued investigation of an abnormality in serotonergic function in this syndrome. Previously we showed that the tricyclic antidepressant clomipramine was specifically anti-obsessional, in contrast to several other antidepressants. As clomipramine is considerably more potent than other tricyclic antidepressants in its serotonergic effects, we hypothesized that drugs with selective actions on serotonin receptors would affect obsessional symptoms. Indeed, administration of the selective serotonin postsynaptic receptor agonist m-chlorophenylpiperazine (m-CPP) appeared to increase obsessional symptoms and anxiety in patients with obsessive-compulsive disorder but not in healthy controls. By contrast, the post-synaptic serotonin receptor antagonist, metergoline was associated with a slight decrease in obsessional symptoms. The obsession-inducing effects of m-CPP appear to be blocked by chronic clomipramine administration.

Continued studies of cerebral blood flow in obsessive-compulsive patients have revealed an increase in cortical flow during "imaginal flooding" and a profound decrease in cortical flow during actual exposure to the obsessional stimulus.

Finally, we continue to track the natural course of this disorder with follow-up studies of patients treated between 1980-1983.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 00337-07 LCS

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Neuropharmacology of Neuroendocrine and Neurotransmitter Regulatory Mechanisms

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dennis L. Murphy, M.D., Chief, Section on Clinical Neuropharmacology, LCS, NIMH

COOPERATING UNITS *(if any)*
Centre for Reproductive Biology, Edinburgh, Scotland; LN, NIMH; HEB, NIMH; NIB, NINCDS

LAB/BRANCH
Laboratory of Clinical Science

SECTION
Section on Clinical Neuropharmacology

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.1	2.0	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.)*

M-Clorophenylpiperazine (m-CPP), a direct serotonin receptor agonist, has been studied extensively this year by our group in rodents, monkeys and, for the first time, in humans. In normal volunteers, m-CPP's neuroendocrine effects on prolactin and cortisol exhibited a clear dose-dependent relationship. These changes were blocked by the serotonin receptor antagonist, metergoline. M-clorophenylpiperazine also elicited changes in temperature, behavior and adrenocorticotropin release. Studies using m-CPP as a probe of serotonin CNS function in different psychiatric patient groups and during psychoactive drug treatment conditions are underway.

Marked effects of antidepressant drugs, especially MAO-inhibitors, have been observed on plasma and cerebrospinal fluid melatonin and serotonin concentrations in monkeys and humans.

The localization of a number of neuropeptides, including atrial natriuretic peptide, enkephalins, metorphamide and melanin concentrating hormone has been delineated in rodent brain.

Antibodies to β-endorphin have been identified and characterized in human plasma.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 00337-07 LCS

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT (80 characters or less. Title must fit on one line between the borders.)
Neuropharmacology of Neuroendocrine and Neurotransmitter Regulatory Mechanisms

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)

Dennis L. Murphy, M.D., Chief, Section on Clinical Neuropharmacology, LCS, NIMH

COOPERATING UNITS (if any)
Centre for Reproductive Biology, Edinburgh, Scotland; LN, NIMH; HEB, NIMH; NIB, NINCDS

LAB/BRANCH
Laboratory of Clinical Science

SECTION
Section on Clinical Neuropharmacology

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.1	2.0	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.)

M-Clorophenylpiperazine (m-CPP), a direct serotonin receptor agonist, has been studied extensively this year by our group in rodents, monkeys and, for the first time, in humans. In normal volunteers, m-CPP's neuroendocrine effects on prolactin and cortisol exhibited a clear dose-dependent relationship. These changes were blocked by the serotonin receptor antagonist, metergoline. M-clorophenylpiperazine also elicited changes in temperature, behavior and adrenocorticotropin release. Studies using m-CPP as a probe of serotonin CNS function in different psychiatric patient groups and during psychoactive drug treatment conditions are underway.

Marked effects of antidepressant drugs, especially MAO-inhibitors, have been observed on plasma and cerebrospinal fluid melatonin and serotonin concentrations in monkeys and humans.

The localization of a number of neuropeptides, including atrial natriuretic peptide, enkephalins, metorphamide and melanin concentrating hormone has been delineated in rodent brain.

Antibodies to β-endorphin have been identified and characterized in human plasma.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00339-05 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Neuropharmacology of Cognition and Mood in Geriatric Neuropsychiatry

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Trey Sunderland, Staff Physician LCS, NIMH

COOPERATING UNITS *(if any)*

LCM, NIMH; NIDA;
Enzor Research Foundation

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Clinical Neuropharmacology

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.3	2.0	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.)*

Previous work from this unit has focused on the cognitive and behavioral responses of Alzheimer patients to pharmacologic challenges with cholinergic and opiate antagonists. We observed that the dementia patients appeared more sensitive to these antagonists (scopolamine and naloxone) than previously reported in younger controls. This year, we have demonstrated that behavioral and cognitive responses (but not physiologic changes) following scopolamine are indeed greater at lower doses in Alzheimer patients than in age-matched controls, suggesting increased sensitivity in this population with known cholinergic deficits. We are now in the process of completing a similar comparison using naloxone in age-matched normal volunteers. Expanded studies of the cognitive, behavioral and neuroendocrine responses of Alzheimer patients to cholinergic agonists such as arecholine and nicotine are also underway.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00339-05 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Neuropharmacology of Cognition and Mood in Geriatric Neuropsychiatry

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Trey Sunderland, Staff Physician LCS, NIMH

COOPERATING UNITS *(if any)*

LCM, NIMH; NIDA;
Enzor Research Foundation

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Clinical Neuropharmacology

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.3	2.0	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.)*

Previous work from this unit has focused on the cognitive and behavioral responses of Alzheimer patients to pharmacologic challenges with cholinergic and opiate antagonists. We observed that the dementia patients appeared more sensitive to these antagonists (scopolamine and naloxone) than previously reported in younger controls. This year, we have demonstrated that behavioral and cognitive responses (but not physiologic changes) following scopolamine are indeed greater at lower doses in Alzheimer patients than in age-matched controls, suggesting increased sensitivity in this population with known cholinergic deficits. We are now in the process of completing a similar comparison using naloxone in age-matched normal volunteers. Expanded studies of the cognitive, behavioral and neuroendocrine responses of Alzheimer patients to cholinergic agonists such as arecholine and nicotine are also underway.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00425-10 LCS

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Peripheral and Central Catecholamines in Hypertension and Stress

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Juan M. Saavedra, M.D. Chief, Unit on Preclinical Neuropharmacology
Section on Clinical Pharmacology LCS, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Clinical Pharmacology

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.9	1.5	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 has merged with Z01 MH 00433-06 LCS.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00425-10 LCS

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Peripheral and Central Catecholamines in Hypertension and Stress

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Juan M. Saavedra, M.D. Chief, Unit on Preclinical Neuropharmacology
Section on Clinical Pharmacology LCS, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Clinical Pharmacology

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.9	1.5	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 has merged with Z01 MH 00433-06 LCS.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00428-07 LCS

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Protein Carboxyl Methylation: A Post Translational Modifier of Protein Function

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Juan M. Saavedra, M.D. Chief, Unit on Preclinical Neuropharmacology
Section on Clinical Pharmacology LCS, NIMH

Others: None

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Clinical Pharmacology

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
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.)*

This project is temporarily inactive due to a shift of priorities to other projects.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00428-07 LCS

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Protein Carboxyl Methylation: A Post Translational Modifier of Protein Function

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Juan M. Saavedra, M.D. Chief, Unit on Preclinical Neuropharmacology
Section on Clinical Pharmacology LCS, NIMH

Others: None

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Clinical Pharmacology

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
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.)*

This project is temporarily inactive due to a shift of priorities to other projects.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 00433-06 LCS

PERIOD COVERED
October 1, 1985 through September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Role of Neuropeptides and Biogenic Amines in Neuroendocrine Regulation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Juan M. Saavedra, M.D. Chief, Unit on Preclinical Neuropharmacology
Section on Clinical Pharmacology LCS, NIMH

Others: See Attached Sheet

COOPERATING UNITS *(if any)*
Hypertension-Endocrine Branch, NHLBI; NIGMS; Experimental Therapeutics Branch, NINCDS

LAB/BRANCH
Laboratory of Clinical Science

SECTION
Section on Clinical Pharmacology

INSTITUTE AND LOCATION
NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.0	4.4	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.)*

We studied the role of several neuropeptides (angiotensin II, atrial natriuretic factor, substance P) and biogenic amines (dopamine, norepinephrine, serotonin) in the central regulation of the functions of the autonomic nervous system and the pituitary gland. Special emphasis was given to central cardiovascular control and the central control of fluid metabolism.

The metabolism of biogenic amines in individual brain nuclei was studied by radioenzymatic assays and by high pressure liquid chromatography. Neuropeptide content of brain nuclei was studied by radioimmunoassays. Neuropeptide and biogenic amine receptors were studied in individual brain nuclei by quantitative autoradiographic methods with computerized microdensitometry and comparison to ^{125}I-standards. Animal models included the spontaneously (genetic) hypertensive rat (SHR), the Brattleboro rat, unable to synthesize vasopressin, neurogenically hypertensive rats (sinoaortic denervated), acutely dehydrated rats and adrenolectomized, adrenodemedulectomized and hypophysectomized rats.

We demonstrated a central role for angiotensin II and atrial natriuretic factor in genetic hypertension and dehydration, and a role for the biogenic amines, dopamine, norepinephrine, and serotonin in genetic hypertension and in the regulation of circadian rhythms.

This project also incorporates work previously reported under project Z01 MH 00425-10 LCS.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00433-06 LCS

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Role of Neuropeptides and Biogenic Amines in Neuroendocrine Regulation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Juan M. Saavedra, M.D. Chief, Unit on Preclinical Neuropharmacology
Section on Clinical Pharmacology LCS, NIMH

Others: See Attached Sheet

COOPERATING UNITS *(if any)*

Hypertension-Endocrine Branch, NHLBI; NIGMS; Experimental Therapeutics Branch, NINCDS

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Clinical Pharmacology

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.0	4.4	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.)*

We studied the role of several neuropeptides (angiotensin II, atrial natriuretic factor, substance P) and biogenic amines (dopamine, norepinephrine, serotonin) in the central regulation of the functions of the autonomic nervous system and the pituitary gland. Special emphasis was given to central cardiovascular control and the central control of fluid metabolism.

The metabolism of biogenic amines in individual brain nuclei was studied by radioenzymatic assays and by high pressure liquid chromatography. Neuropeptide content of brain nuclei was studied by radioimmunoassays. Neuropeptide and biogenic amine receptors were studied in individual brain nuclei by quantitative autoradiographic methods with computerized microdensitometry and comparison to ^{125}I-standards. Animal models included the spontaneously (genetic) hypertensive rat (SHR), the Brattleboro rat, unable to synthesize vasopressin, neurogenically hypertensive rats (sinoaortic denervated), acutely dehydrated rats and adrenolectomized, adrenodemedulectomized and hypophysectomized rats.

We demonstrated a central role for angiotensin II and atrial natriuretic factor in genetic hypertension and dehydration, and a role for the biogenic amines, dopamine, norepinephrine, and serotonin in genetic hypertension and in the regulation of circadian rhythms.

This project also incorporates work previously reported under project Z01 MH 00425-10 LCS.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 00447-17 LCS

PERIOD COVERED
October 1, 1985, through September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Amine neurotransmitters and metabolites in mental illness

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

William Z. Potter, M.D., Ph.D., Chief, Section on Clinical Pharmacology, Laboratory of Clinical Science, NIMH

COOPERATING UNITS *(if any)*
Clinical Psychobiology Branch; Neuroscience Branch; Child Psychiatry Branch, NIMH; and Laboratory of Clinical Studies, NIAAA

LAB/BRANCH
Laboratory of Clinical Science

SECTION
Section on Clinical Pharmacology

INSTITUTE AND LOCATION
NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.9	3.0	.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.)*

Alterations of amine neurotransmitter systems (norepinephrine (NE), serotonin (5HT) and dopamine (DA)) have been indirectly implicated in the pathophysiology of the major mental illnesses, depression and schizophrenia. We have applied new techniques to study cerebrospinal fluid (CSF), plasma and urine from drug-free patients with affective illness and schizophrenia using more sensitive and comprehensive characterization of the neurotransmitter systems as well as selective measures of post-synaptic function. New findings include the following:

1. The relationship between neurotransmitter systems, especially 5HT and DA, as measured by their major metabolites may be a marker of treatment response rather than absolute levels per se. There is also an important positive correlation between the NE metabolite and those of 5HT and DA. Data best fit a model whereby the strongest average influence is of the 5HT system on the DA one. Among a substantial group of seriously depressed patients, the only predictor of response was whether the 5HIAA/HVA correlation was high and similar to that observed in control subjects (good response) or was very weak (poor response).

2. Dysregulation of the noradrenergic system is the most consistently observed abnormality in depressed patients either as indexed by plasma NE response or shifts in the relative excretion of NE and its metabolites in urine. This, however, does not predict treatment response although it may distinguish unipolar from bipolar patients.

3. Direct measures of NE and its metabolites under resting vs stimulated conditions provide critical data that cannot be replaced or substituted for by such postsynaptic measures as beta receptors on lymphocytes or hydroxy melatonin output.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00447-17 LCS

PERIOD COVERED

October 1, 1985, through September 30, 1986

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

Amine neurotransmitters and metabolites in mental illness

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

William Z. Potter, M.D., Ph.D., Chief, Section on Clinical Pharmacology, Laboratory of Clinical Science, NIMH

COOPERATING UNITS *(if any)*

Clinical Psychobiology Branch; Neuroscience Branch; Child Psychiatry Branch, NIMH; and Laboratory of Clinical Studies, NIAAA

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Clinical Pharmacology

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.9	3.0	.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.)*

Alterations of amine neurotransmitter systems (norepinephrine (NE), serotonin (5HT) and dopamine (DA)) have been indirectly implicated in the pathophysiology of the major mental illnesses, depression and schizophrenia. We have applied new techniques to study cerebrospinal fluid (CSF), plasma and urine from drug-free patients with affective illness and schizophrenia using more sensitive and comprehensive characterization of the neurotransmitter systems as well as selective measures of post-synaptic function. New findings include the following:

1. The relationship between neurotransmitter systems, especially 5HT and DA, as measured by their major metabolites may be a marker of treatment response rather than absolute levels per se. There is also an important positive correlation between the NE metabolite and those of 5HT and DA. Data best fit a model whereby the strongest average influence is of the 5HT system on the DA one. Among a substantial group of seriously depressed patients, the only predictor of response was whether the 5HIAA/HVA correlation was high and similar to that observed in control subjects (good response) or was very weak (poor response).

2. Dysregulation of the noradrenergic system is the most consistently observed abnormality in depressed patients either as indexed by plasma NE response or shifts in the relative excretion of NE and its metabolites in urine. This, however, does not predict treatment response although it may distinguish unipolar from bipolar patients.

3. Direct measures of NE and its metabolites under resting vs stimulated conditions provide critical data that cannot be replaced or substituted for by such postsynaptic measures as beta receptors on lymphocytes or hydroxy melatonin output.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01850-09 LCS

PERIOD COVERED

October 1, 1985, through September 30, 1986

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

Clinical pharmacology of antidepressants

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

William Z. Potter, M.D., Ph.D., Chief, Section on Clinical Pharmacology, Laboratory of Clinical Science, NIMH

COOPERATING UNITS *(if any)*

Clinical Psychobiology Branch; Clinical Neuroscience Branch; and Laboratory of Clinical Studies, NIAAA

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Clinical Pharmacology

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.6	4.3	1.3

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 therapeutic mechanism of action of antidepressant medications in humans remains unknown. Comparison of effects on specific neurotransmitters and their metabolites in cerebrospinal fluid (CSF), plasma and urine in the same patients continues and is complemented by physiologic, behavioral and neuroendocrine measures, allowing for clearer systems interpretations of changes. Recent findings of particular interest include the following:

1. We have identified unique biochemical changes in patients treated with electroconvulsive therapy (ECT) compared to antidepressant drugs. Although all active antidepressant treatments we have studied reduce norepinephrine (NE) turnover, only ECT increases CSF concentrations of 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of serotonin and homovanillic acid (HVA), the main dopamine metabolite.
2. Building upon our findings of common noradrenergic effects of biochemically disparate antidepressant treatments, we have investigated the relationships among various neurotransmitter systems in depressed patients before and after treatment. Characteristic patterns of changes not only in absolute but also relative concentrations of transmitter substances, e.g. HVA/5-HIAA ratio in CSF, are emerging in response to various interventions.
3. Several types of antidepressant drugs increase excretion of 6-hydroxymelatonin. Opposite results with the monoamine oxidase (MAO) type A inhibitor, clorgyline, in some patients, are consistent with the melatonin measure's relating to peripheral, rather than central, sympathetic nervous system activity.
4. Utilizing intravenous clomipramine in single doses small enough to maintain selective serotonin reuptake inhibition, diminished serotonergic function in depression, as reflected in blunted serum prolactin response, is seen in a preliminary comparison of patients and healthy volunteers.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01850-09 LCS

PERIOD COVERED

October 1, 1985, through September 30, 1986

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

Clinical pharmacology of antidepressants

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

William Z. Potter, M.D., Ph.D., Chief, Section on Clinical Pharmacology, Laboratory of Clinical Science, NIMH

COOPERATING UNITS *(if any)*

Clinical Psychobiology Branch; Clinical Neuroscience Branch; and Laboratory of Clinical Studies, NIAAA

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Clinical Pharmacology

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.6	4.3	1.3

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 therapeutic mechanism of action of antidepressant medications in humans remains unknown. Comparison of effects on specific neurotransmitters and their metabolites in cerebrospinal fluid (CSF), plasma and urine in the same patients continues and is complemented by physiologic, behavioral and neuroendocrine measures, allowing for clearer systems interpretations of changes. Recent findings of particular interest include the following:

1. We have identified unique biochemical changes in patients treated with electroconvulsive therapy (ECT) compared to antidepressant drugs. Although all active antidepressant treatments we have studied reduce norepinephrine (NE) turnover, only ECT increases CSF concentrations of 5-hydroxyindoleacetic acid (5-HIAA), the major metabolite of serotonin and homovanillic acid (HVA), the main dopamine metabolite.
2. Building upon our findings of common noradrenergic effects of biochemically disparate antidepressant treatments, we have investigated the relationships among various neurotransmitter systems in depressed patients before and after treatment. Characteristic patterns of changes not only in absolute but also relative concentrations of transmitter substances, e.g. HVA/5-HIAA ratio in CSF, are emerging in response to various interventions.
3. Several types of antidepressant drugs increase excretion of 6-hydroxymelatonin. Opposite results with the monoamine oxidase (MAO) type A inhibitor, clorgyline, in some patients, are consistent with the melatonin measure's relating to peripheral, rather than central, sympathetic nervous system activity.
4. Utilizing intravenous clomipramine in single doses small enough to maintain selective serotonin reuptake inhibition, diminished serotonergic function in depression, as reflected in blunted serum prolactin response, is seen in a preliminary comparison of patients and healthy volunteers.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01855-02 LCS

PERIOD COVERED

October 1, 1985, through September 30, 1986

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

Central Neurochemistry Service

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

William Z. Potter, M.D., Ph.D., Chief, Section on Clinical Pharmacology, Laboratory of Clinical Science, NIMH

COOPERATING UNITS *(if any)*

Section on Analytical Biochemistry and Section on Biomedical Psychiatry, LCS, NIMH; Laboratory of Clinical Studies, NIAAA

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Clinical Pharmacology

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.1	1.0	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 Central Neurochemistry Service functions as a centralized laboratory for analysis of neurotransmitters and metabolites in body fluids collected within the intramural program. Routine analyses include norepinephrine in plasma, urine and CSF, epinephrine in urine and plasma, dopamine and dopamine sulfate in urine, plasma and CSF, catecholamine metabolites, HVA, MHPG and DOPAC in CSF, plasma and urine, serotonin in platelets and platelet poor plasma and 5HIAA in plasma, CSF and urine. GC-MS assays are used for total urinary norepinephrine, epinephrine and dopamine and urinary VMA, MHPG and normetanephrine. HPLC with electrochemical detection is used for other analyses. Modifications of existing procedures allow simultaneous determination of HVA, 5HIAA and MHPG in plasma. This allows simultaneous observation of drug and/or diurnal effects on metabolites of three different neurotransmitter systems. Over 8500 assays were performed on over 6000 samples which were processed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01855-02 LCS

PERIOD COVERED

October 1, 1985, through September 30, 1986

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

Central Neurochemistry Service

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

William Z. Potter, M.D., Ph.D., Chief, Section on Clinical Pharmacology, Laboratory of Clinical Science, NIMH

COOPERATING UNITS *(if any)*

Section on Analytical Biochemistry and Section on Biomedical Psychiatry, LCS, NIMH; Laboratory of Clinical Studies, NIAAA

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Clinical Pharmacology

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.1	1.0	3.1

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.)*

The Central Neurochemistry Service functions as a centralized laboratory for analysis of neurotransmitters and metabolites in body fluids collected within the intramural program. Routine analyses include norepinephrine in plasma, urine and CSF, epinephrine in urine and plasma, dopamine and dopamine sulfate in urine, plasma and CSF, catecholamine metabolites, HVA, MHPG and DOPAC in CSF, plasma and urine, serotonin in platelets and platelet poor plasma and 5HIAA in plasma, CSF and urine. GC-MS assays are used for total urinary norepinephrine, epinephrine and dopamine and urinary VMA, MHPG and normetanephrine. HPLC with electrochemical detection is used for other analyses. Modifications of existing procedures allow simultaneous determination of HVA, 5HIAA and MHPG in plasma. This allows simultaneous observation of drug and/or diurnal effects on metabolites of three different neurotransmitter systems. Over 8500 assays were performed on over 6000 samples which were processed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00787-07 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Brain Mechanisms of Isolation Call in Squirrel Monkey (Saimiri sciureus)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	P. D. MacLean	Intramural Research Scientist	LCS, NIMH
Others:	J. D. Newman	Research Physiologist	LCE, NICHD

COOPERATING UNITS *(if any)*

Laboratory of Comparative Ethology, NICHD

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Comparative Studies of Brain and Behavior

INSTITUTE AND LOCATION

NIMH, NIH, Poolesville, Maryland 20837

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.9	0.5	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 long-term project is concerned with identifying cerebral mechanisms that evolved in association with the development of various forms of vocalization in mammals. For this purpose studies have been made on the effect of various cerebral lesions on the production of the isolation call (separation cry) which perhaps represents the oldest and most basic mammalian vocalization, serving originally to maintain maternal-offspring contact and then, additionally, contact among members of a group. Adult squirrel monkeys are used in the present studies. The two main types of these monkeys identified as gothic or roman on the basis of the arch formed by the ocular patch, produce individually distinct isolation calls both as infants and adults. Monkeys of either type and of either sex are tested for their ability to produce isolation calls before and after destruction of different parts of the brain. Criterion performance is established as the production of 20 or more isolation calls during a 15-minute period of isolation in a sound-reducing chamber. Sound spectrography is used as a means of detecting changes in structure of the calls. Experiments reported in last year's report revealed that the spontaneous production of the isolation call depends on the concerted action of a continuous band of midline frontal limbic cortex. This year's work has dealt with the question of interdependence of the midline frontal neocortex and limbic cortex in the production of the call. It was found that aspiration of all the midline frontal cortex peripheral to the crucial band of limbic cortex was not essential for the spontaneous production of the call and that incidental damage to N. accumbens was not a factor.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00787-07 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Brain Mechanisms of Isolation Call in Squirrel Monkey (Saimiri sciureus)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	P. D. MacLean	Intramural Research Scientist	LCS, NIMH
Others:	J. D. Newman	Research Physiologist	LCE, NICHD

COOPERATING UNITS *(if any)*

Laboratory of Comparative Ethology, NICHD

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Comparative Studies of Brain and Behavior

INSTITUTE AND LOCATION

NIMH, NIH, Poolesville, Maryland 20837

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.9	0.5	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 long-term project is concerned with identifying cerebral mechanisms that evolved in association with the development of various forms of vocalization in mammals. For this purpose studies have been made on the effect of various cerebral lesions on the production of the isolation call (separation cry) which perhaps represents the oldest and most basic mammalian vocalization, serving originally to maintain maternal-offspring contact and then, additionally, contact among members of a group. Adult squirrel monkeys are used in the present studies. The two main types of these monkeys identified as gothic or roman on the basis of the arch formed by the ocular patch, produce individually distinct isolation calls both as infants and adults. Monkeys of either type and of either sex are tested for their ability to produce isolation calls before and after destruction of different parts of the brain. Criterion performance is established as the production of 20 or more isolation calls during a 15-minute period of isolation in a sound-reducing chamber. Sound spectrography is used as a means of detecting changes in structure of the calls. Experiments reported in last year's report revealed that the spontaneous production of the isolation call depends on the concerted action of a continuous band of midline frontal limbic cortex. This year's work has dealt with the question of interdependence of the midline frontal neocortex and limbic cortex in the production of the call. It was found that aspiration of all the midline frontal cortex peripheral to the crucial band of limbic cortex was not essential for the spontaneous production of the call and that incidental damage to N. accumbens was not a factor.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00795-02 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Comparative Cytoarchitecture of the Cingulate Cortex

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: P.D. MacLean Intramural Research Scientist LCS, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Comparative Studies of Brain and Behavior

INSTITUTE AND LOCATION

NIMH, NIH, Poolesville, Maryland 20837

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.3	0.1	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.)*

This project was inactive this year due to difficulties in obtaining exotic animals for study. The principal investigator plans to reactivate this project when possible in the future.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00795-02 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Comparative Cytoarchitecture of the Cingulate Cortex

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: P.D. MacLean Intramural Research Scientist LCS, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Comparative Studies of Brain and Behavior

INSTITUTE AND LOCATION

NIMH, NIH, Poolesville, Maryland 20837

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.3	0.1	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.)*

This project was inactive this year due to difficulties in obtaining exotic animals for study. The principal investigator plans to reactivate this project when possible in the future.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00796-01 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Cytochemical Tracing of Thalamic Connections with Midline Frontal Cortex

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: P. D. MacLean Intramural Research Scientist LCS, NIMH

Others:

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Comparative Studies of Brain and Behavior

INSTITUTE AND LOCATION

NIMH, NIH, Poolesville, Maryland 20837

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.85	0.5	0.35

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 an accompanying project concerned with the cerebral representation of the isolation call, it was found that bilateral ablations of the midline frontal cortex did not result in definitive retrograde degeneration in the thalamus of squirrel monkeys. The lack of such degeneration has been classically recognized in rhesus monkeys. In ongoing studies of the differential effects of ablations of the frontal midline neocortex and limbic cortex it is of basic importance to clarify the question in regard to afferent connections from the thalamus. Application of an improved technique employing wheat germ agglutinin conjugated to horseradish peroxidase (WGA-HRP) is being used for this purpose. Thus far, application of WGA-HRP to the pregenual and subcallosal limbic cortex has been found to result in conspicuous labeling in the rostral parts of N. anterior ventralis et medialis, N. centralis medialis; N. reuniens; N. ventralis anterior; N. ventralis lateralis medialis; N. paraventricularis; the N. parataenialis and N. centralis superior lateralis, together with the underlying part of N. medialis dorsalis; parts of N. parafascicularis and N. centralis lateralis; the medial protrusion of N. pulvinar medialis; and N. limitans. The several sites of extrathalamic labeling are given in the full report. Considered in the light of experimental and clinical data, the thalamic findings suggest a link-up of frontal lobe and striopallidonigral mechanisms implicated in both the affect and expression of crying and laughter.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 00796-01 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Cytochemical Tracing of Thalamic Connections with Midline Frontal Cortex

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: P. D. MacLean Intramural Research Scientist LCS, NIMH

Others:

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Comparative Studies of Brain and Behavior

INSTITUTE AND LOCATION

NIMH, NIH, Poolesville, Maryland 20837

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.85	0.5	0.35

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 an accompanying project concerned with the cerebral representation of the isolation call, it was found that bilateral ablations of the midline frontal cortex did not result in definitive retrograde degeneration in the thalamus of squirrel monkeys. The lack of such degeneration has been classically recognized in rhesus monkeys. In ongoing studies of the differential effects of ablations of the frontal midline neocortex and limbic cortex it is of basic importance to clarify the question in regard to afferent connections from the thalamus. Application of an improved technique employing wheat germ agglutinin conjugated to horseradish peroxidase (WGA-HRP) is being used for this purpose. Thus far, application of WGA-HRP to the pregenual and subcallosal limbic cortex has been found to result in conspicuous labeling in the rostral parts of N. anterior ventralis et medialis, N. centralis medialis; N. reuniens; N. ventralis anterior; N. ventralis lateralis medialis; N. paraventricularis; the N. parataenialis and N. centralis superior lateralis, together with the underlying part of N. medialis dorsalis; parts of N. parafascicularis and N. centralis lateralis; the medial protrusion of N. pulvinar medialis; and N. limitans. The several sites of extrathalamic labeling are given in the full report. Considered in the light of experimental and clinical data, the thalamic findings suggest a link-up of frontal lobe and striopallidonigral mechanisms implicated in both the affect and expression of crying and laughter.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00797-01 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Neurobiology of Attachment

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	T. R. Insel	Staff Physician	LCS	NIMH
Others:	G. E. Handelmann	Sr. Staff Fellow	LCS	NIMH
	J. L. Hill	Guest Worker	LCS	NIMH
	M. Z. Wamboldt	Staff Physician	LCS	NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Clinical Science, NIMH

SECTION

Section on Comparative Studies of Brain and Behavior

INSTITUTE AND LOCATION

NIMH, NIH, Poolesville, Maryland 20837

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	1.3	0.7

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.)*

This is the first year of this project which uses a comparative approach to investigate attachment and separation in both infants and parents. Studies in rodents have characterized the ultrasonic isolation call in 1-week-old pups and shown that benodiazepine, adrenergic and opiate receptor ligands have potent effects on this behavior. In studies of parental care, oxytocin was found to induce maternal behavior in anosmic nulliparous, virgin females. Autoradiographic analysis of oxytocin receptors in rat brain revealed a discrete increase in the bed nucleus of the stria terminalis in lactating females. This local induction of oxytocin receptors was reproduced in virgin ovariectomized females by acute administration of estrogen, a treatment that simulates the endocrine milieu just prior to parturition. Studies in pygmy marmosets (Cebuella pygmaea) yielded one of the first quantitative descriptions of a non-human primate in which the male provides most of the parental care. Semi-naturalistic observational studies of this phenomenon were replicated in a controlled, prospective design. During this first year two other studies were begun: one studying the changes in CSF peptides before and after parturition in rhesus monkeys and a second analyzing peptide and steroid content in the milk of various mammals including humans.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00797-01 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Neurobiology of Attachment

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	T. R. Insel	Staff Physician	LCS	NIMH
Others:	G. E. Handelmann	Sr. Staff Fellow	LCS	NIMH
	J. L. Hill	Guest Worker	LCS	NIMH
	M. Z. Wamboldt	Staff Physician	LCS	NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Clinical Science, NIMH

SECTION

Section on Comparative Studies of Brain and Behavior

INSTITUTE AND LOCATION

NIMH, NIH, Poolesville, Maryland 20837

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	1.3	0.7

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.)*

This is the first year of this project which uses a comparative approach to investigate attachment and separation in both infants and parents. Studies in rodents have characterized the ultrasonic isolation call in 1-week-old pups and shown that benodiazepine, adrenergic and opiate receptor ligands have potent effects on this behavior. In studies of parental care, oxytocin was found to induce maternal behavior in anosmic nulliparous, virgin females. Autoradiographic analysis of oxytocin receptors in rat brain revealed a discrete increase in the bed nucleus of the stria terminalis in lactating females. This local induction of oxytocin receptors was reproduced in virgin ovariectomized females by acute administration of estrogen, a treatment that simulates the endocrine milieu just prior to parturition. Studies in pygmy marmosets (Cebuella pygmaea) yielded one of the first quantitative descriptions of a non-human primate in which the male provides most of the parental care. Semi-naturalistic observational studies of this phenomenon were replicated in a controlled, prospective design. During this first year two other studies were begun: one studying the changes in CSF peptides before and after parturition in rhesus monkeys and a second analyzing peptide and steroid content in the milk of various mammals including humans.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00851-22

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Brain Mechanisms of Display Behavior in Squirrel Monkey (Saimiri sciureus)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	P.D. MacLean	Intramural Research Scientist	LCS, NIMH
Others:	J.D. Newman	Research Physiologist	LCE, NICHD

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Comparative Studies of Brain and Behavior

INSTITUTE AND LOCATION

NIMH, NIH, Poolesville, Maryland 20837

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.9	0.5	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 was inactivated early in the year and subsequently terminated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00851-22

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Brain Mechanisms of Display Behavior in Squirrel Monkey (Saimiri sciureus)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	P.D. MacLean	Intramural Research Scientist	LCS, NIMH
Others:	J.D. Newman	Research Physiologist	LCE, NICHD

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Section on Comparative Studies of Brain and Behavior

INSTITUTE AND LOCATION

NIMH, NIH, Poolesville, Maryland 20837

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.9	0.5	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 was inactivated early in the year and subsequently terminated.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02219-03 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Animal Models of Anxiety

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: T. R. Insel Staff Physician LCS, NIMH

COOPERATING UNITS *(if any)*

Biological Psychiatry Branch, NIMH; Laboratory of Comparative Ethology, NICHD; Addiction Research Center, NIDA, Baltimore, MD

LAB/BRANCH

Laboratory of Clinical Science, NIMH

SECTION

Section on Comparative Studies of Brain and Behavior

INSTITUTE AND LOCATION

NIMH, NIH, Poolesville, Maryland 20837

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	0.7	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.)*

Our approach to the neurobiology of anxiety has become increasingly developmental with a focus on both genetic components (using inbred strains) and the contribution of early experience (using diverse rearing conditions).

Inbred rat strains selected for emotional reactivity--the Maudsley reactive and non-reactive strains--showed no differences in brain benzodiazepine receptor binding, but could be distinguished by the number of adenosine receptors in the molecular layer of the cerebellum. Preliminary data suggest higher levels of norepinephrine in the frontal cortex and the locus coeruleus of the reactive strain.

The importance of rearing condition was demonstrated in rhesus monkeys raised with or without control over appetitive (non-aversive) stimuli. This "mastery-yoked" paradigm was employed throughout the first year of life for animals raised in peer groups. Two years later the "mastery" animals--i.e. those raised with control over toys and food treats--showed less distress when isolated in comparison to individuals reared in the "yoked" condition--who received identical toys and treats on a non-contingent basis. Following administration of the benzodiazepine receptor inverse agonist β-CCE, mastery animals appeared hostile whereas yoked animals appeared fearful and withdrawn.

Using in vitro receptor autoradiography, brain receptors for both corticotropin releasing factor (CRF) and benzodiazepines were first found at 17 days gestation in the rat (i.e. 4 days prior to birth). As other peptide hormones when administered early in life can have long-term consequences on behavior and neural receptor sensitivity, we investigated the results of CRF administration during the first week of life. Rat pups given CRF daily from day 1-7 were not consistently more emotionally reactive behaviorally, but showed increased corticosterone levels following isolation in adulthood.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02219-03 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Animal Models of Anxiety

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: T. R. Insel Staff Physician LCS, NIMH

COOPERATING UNITS *(if any)*

Biological Psychiatry Branch, NIMH; Laboratory of Comparative Ethology, NICHD; Addiction Research Center, NIDA, Baltimore, MD

LAB/BRANCH

Laboratory of Clinical Science, NIMH

SECTION

Section on Comparative Studies of Brain and Behavior

INSTITUTE AND LOCATION

NIMH, NIH, Poolesville, Maryland 20837

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	0.7	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.)*

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00382-12 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Localization and Characterization of Brain Neuropeptides

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

David M. Jacobowitz	Chief, Histopharmacology Section	LCS, NIMH
Gerhard Skofitsch	Guest Worker	LCS, NIMH
Nadav Zamir	Visiting Associate	HE, NHLBI

COOPERATING UNITS *(if any)*

Hypertension and Endocrine Branch, National Heart, Lung and Blood Institute

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Histopharmacology

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.7	1.3	.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.)*

(1) Using radioimmunoassay (RIA) and the micropunch technique quantitative distribution of the brain neuropeptides atrial natriuretic factor (ANF) and galanin (GAL) in discrete brain nuclei were determined. The widespread distribution of these peptides in the rat CNS suggests an involvement of GAL and ANF in a variety of brain functions. (2) The autoradiographic distribution of GAL receptor sites in the rat brain has been demonstrated. (3) The immunohistochemical distribution of ANF, GAL and calcitonin gene-related peptide (CGRP) has been mapped in the subnuclei of the interpeduncular nuclei. This work lays the groundwork for further studies on the functional role of these brain neuropeptides (ANF, GAL, CGRP) in the CNS.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00382-12 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Localization and Characterization of Brain Neuropeptides

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

David M. Jacobowitz	Chief, Histopharmacology Section	LCS, NIMH
Gerhard Skofitsch	Guest Worker	LCS, NIMH
Nadav Zamir	Visiting Associate	HE, NHLBI

COOPERATING UNITS *(if any)*

Hypertension and Endocrine Branch, National Heart, Lung and Blood Institute

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Histopharmacology

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.7	1.3	.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.)*

(1) Using radioimmunoassay (RIA) and the micropunch technique quantitative distribution of the brain neuropeptides atrial natriuretic factor (ANF) and galanin (GAL) in discrete brain nuclei were determined. The widespread distribution of these peptides in the rat CNS suggests an involvement of GAL and ANF in a variety of brain functions. (2) The autoradiographic distribution of GAL receptor sites in the rat brain has been demonstrated. (3) The immunohistochemical distribution of ANF, GAL and calcitonin gene-related peptide (CGRP) has been mapped in the subnuclei of the interpeduncular nuclei. This work lays the groundwork for further studies on the functional role of these brain neuropeptides (ANF, GAL, CGRP) in the CNS.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00388-10 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Coexistence of Peptides and Neurotransmitters

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

David M. Jacobowitz	Chief, Histopharmacology Section	LCS, NIMH
Gerhard Skofitsch	Guest Worker	LCS, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Histopharmacology

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.6	1.2	.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.)*

We have found a newly discovered peptide, galanin, to be widely distributed in the rat central nervous system (CNS). All cells in the locus coeruleus contain galanin and therefore coexist with norepinephrine-containing nerves that project to the cortex, hippocampus, thalamus, parts of the hypothalamus and spinal cord. The coexistence of galanin and norepinephrine in catecholaminergic nerves suggests that galanin might be involved in a neuroregulatory role at the site of norepinephrine action.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00388-10 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Coexistence of Peptides and Neurotransmitters

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

David M. Jacobowitz	Chief, Histopharmacology Section	LCS, NIMH
Gerhard Skofitsch	Guest Worker	LCS, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Histopharmacology

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.6	1.2	.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.)*

We have found a newly discovered peptide, galanin, to be widely distributed in the rat central nervous system (CNS). All cells in the locus coeruleus contain galanin and therefore coexist with norepinephrine-containing nerves that project to the cortex, hippocampus, thalamus, parts of the hypothalamus and spinal cord. The coexistence of galanin and norepinephrine in catecholaminergic nerves suggests that galanin might be involved in a neuroregulatory role at the site of norepinephrine action.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00396-08 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

A Study of Proteins Within the CNS by Two-Dimensional Gel Electrophoresis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

David M. Jacobowitz	Chief, Histopharmacology Section	LCS, NIMH
William E. Heydorn	Pharmacologist	FDA
Matthew A. Sills	Guest Researcher (NIGMS Fellow)	NIGMS & LCS, NIMH
Raj K. Narayan	Staff Neurosurgeon	SNB, NINCDS
Jorge F. Rodriguez-Sierra	Guest Researcher	LCS, NIMH

COOPERATING UNITS *(if any)*

Division of Neuropharmacological Drug Products, Food and Drug Administration

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Histopharmacology

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.4	2.4	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.)*

A variety of studies of proteins within the CNS utilizing 2-dimensional gel electrophoresis (2DE) continue. First, we have shown that intraventricular injection of the brain with 5HT neurotoxin 5,7-dihydroxytryptamine resulted in a decrease in the concentration of 3 different proteins in the parietal cortex and hippocampus. Two hippocampal proteins were elevated in concentration following 5HT depletion. Second, administration of estradiol to 25 day old female rats resulted in changes in protein concentration of the arcuate nucleus-median eminence complex. We have also identified 21 proteins within this area that are altered in relative turnover rate following estradiol treatment. Third, a variety of human brain tumors were found to have characteristic protein profiles that set it apart from the other tumors studied. Fourth, using immunoblotting and comigration techniques, this study describes the identification of twelve major protein spots seen on 2DE gels of normal cerebral cortex and of certain human brain tumors. Fifth, we have demonstrated that the β-subunit of the G protein from both bovine rod outer segment membranes (transducin) and from bovine brain exists as multiple charge isomers. Sixth, iron deficiency in rats resulted in an increase in the concentration of 3 proteins in the caudate nucleus and one decreased. Neuron specific enolase was elevated in the nucleus accumbens and glial fibrillary acidic protein reduced.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00396-08 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

A Study of Proteins Within the CNS by Two-Dimensional Gel Electrophoresis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

David M. Jacobowitz	Chief, Histopharmacology Section	LCS, NIMH
William E. Heydorn	Pharmacologist	FDA
Matthew A. Sills	Guest Researcher (NIGMS Fellow)	NIGMS & LCS, NIMH
Raj K. Narayan	Staff Neurosurgeon	SNB, NINCDS
Jorge F. Rodriguez-Sierra	Guest Researcher	LCS, NIMH

COOPERATING UNITS *(if any)*

Division of Neuropharmacological Drug Products, Food and Drug Administration

LAB/BRANCH: Laboratory of Clinical Science

SECTION: Histopharmacology

INSTITUTE AND LOCATION: NIMH, ADAMHA, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.4	2.4	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.)*

A variety of studies of proteins within the CNS utilizing 2-dimensional gel electrophoresis (2DE) continue. First, we have shown that intraventricular injection of the brain with 5HT neurotoxin 5,7-dihydroxytryptamine resulted in a decrease in the concentration of 3 different proteins in the parietal cortex and hippocampus. Two hippocampal proteins were elevated in concentration following 5HT depletion. Second, administration of estradiol to 25 day old female rats resulted in changes in protein concentration of the arcuate nucleus-median eminence complex. We have also identified 21 proteins within this area that are altered in relative turnover rate following estradiol treatment. Third, a variety of human brain tumors were found to have characteristic protein profiles that set it apart from the other tumors studied. Fourth, using immunoblotting and comigration techniques, this study describes the identification of twelve major protein spots seen on 2DE gels of normal cerebral cortex and of certain human brain tumors. Fifth, we have demonstrated that the β-subunit of the G protein from both bovine rod outer segment membranes (transducin) and from bovine brain exists as multiple charge isomers. Sixth, iron deficiency in rats resulted in an increase in the concentration of 3 proteins in the caudate nucleus and one decreased. Neuron specific enolase was elevated in the nucleus accumbens and glial fibrillary acidic protein reduced.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00397-08 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Neurophysiological Effects of Peptides

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Matthew A. Sills	Guest Researcher (NIGMS Fellow)	NIGMS & LCS, NIMH
David M. Jacobowitz	Chief, Histopharmacology Section	LCS, NIMH
Toshio Ohhashi	Guest Researcher	LCS, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Histopharmacology

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.3	1.1	.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 purpose of the present studies was to investigate the function and possible clinical relevance of some neuropeptides. Thyrotropin-releasing hormone (TRH) has been suggested in the past to be involved in the mechanism of action of antidepressant compounds. In the present study, we found that repeated administration of either the tricyclic antidepressant desipramine (DMI) or the monoamine oxidase inhibitor nialamide reduced the ability of the TRH analog MK-771 (L-pyro-2-aminoadipyl-histidyl-thiazolidine-4-carboxamide) to induce wet-dog shakes in rats. These results are consistent with the idea that TRH systems are involved in the mechanism of action of antidepressant compounds.

Calcitonin gene-related peptide (CGRP) content as well as CGRP receptors have been shown by our laboratory to be densely localized within the central amygdaloid nucleus (Ce). When CGRP was microinjected into this nucleus, significant increases in both blood pressure (BP) and heart rate (HR) occurred. These results provide a functional correlate for the presence of CGRP and its receptors in the Ce.

Previous studies in our laboratory demonstrated that microinjection of atrial natriuretic peptide (ANP) into the preoptic suprachiasmatic nucleus (POSC) produced significant elevations in both BP and HR. The present studies investigated the mechanism of action of this response to ANP. The results from this study revealed that propranolol inhibited the ANP-induced rise in HR. In addition, atrial peptide fragment (13-28, rat) was found to produce similar changes in BP and HR over a similar time course as atriopeptin III (5-28). These results indicate that the portion of the atrial peptide 5-12 is not essential for central cardiovascular effects to occur, and that the effect on HR by ANP is mediated to some extent by β-adrenergic receptors.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00397-08 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Neurophysiological Effects of Peptides

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Matthew A. Sills	Guest Researcher (NIGMS Fellow)	NIGMS & LCS, NIMH
David M. Jacobowitz	Chief, Histopharmacology Section	LCS, NIMH
Toshio Ohhashi	Guest Researcher	LCS, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH: Laboratory of Clinical Science

SECTION: Histopharmacology

INSTITUTE AND LOCATION: NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.3	1.1	.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.)*

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02239-02 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Conceptual Analysis of Complex Biobehavioral Population Systems.

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: John B. Calhoun Chief URBS, LCS, DIRP, NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Unit for Research on Behavioral Systems

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.00	1.0	2.00

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.)*

By 1973 we had recognized that excessive crowding of mice can culminate in all subjects becoming so autistic that none could exhibit behaviors essential for species survival. We also had developed a technology that recorded the movement of each rat in a population by its identity as it moved through a complex compartmentalized habitat over its lifetime.

These two developments were incorporated into a 1973-1986 set of experimental rodent population studies. Dissolution of residential stability marked the course of origin of an extinction-producing irreversible universal autism, one that might also characterize humans during the next century. Our studies with rats, utilizing the new technology, reveals that acquisition of collaborative social roles modifies contact rate and intensity of status interactions sufficiently to ameliorate pathologies accompanying crowding. A just completed restructuring of the data base of the space-time course of duration and change of behavioral states now permits a more precise delineation of how crowding induces fragmentation of behavior and withdrawal, whereas cooperation leads to longer and more complex behaviors as more effective communication develops.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02239-02 LCS

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Conceptual Analysis of Complex Biobehavioral Population Systems.

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: John B. Calhoun Chief URBS, LCS, DIRP, NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Clinical Science

SECTION

Unit for Research on Behavioral Systems

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.00	1.00	2.00

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.)*

By 1973 we had recognized that excessive crowding of mice can culminate in all subjects becoming so autistic that none could exhibit behaviors essential for species survival. We also had developed a technology that recorded the movement of each rat in a population by its identity as it moved through a complex compartmentalized habitat over its lifetime.

These two developments were incorporated into a 1973-1986 set of experimental rodent population studies. Dissolution of residential stability marked the course of origin of an extinction-producing irreversible universal autism, one that might also characterize humans during the next century. Our studies with rats, utilizing the new technology, reveals that acquisition of collaborative social roles modifies contact rate and intensity of status interactions sufficiently to ameliorate pathologies accompanying crowding. A just completed restructuring of the data base of the space-time course of duration and change of behavioral states now permits a more precise delineation of how crowding induces fragmentation of behavior and withdrawal, whereas cooperation leads to longer and more complex behaviors as more effective communication develops.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00084-12 CNG

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Genetic-Biologic Studies of Psychiatric Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.	E. Gershon	Chief	CNG, NIMH
Others:	L. DeLisi	Staff Psychiatrist	CNG, NIMH
	J.I. Nurnberger, Jr.	Medical Officer	CNG, NIMH
	W.H. Berrettini	Staff Psychiatrist	CNG, NIMH
	J. Hamovit	Research Social Worker	CNG, NIMH
	L. Goldin	Senior Staff Fellow	CNG, NIMH
	J. Baumgold	Research Chemist	CNG, NIMH

COOPERATING UNITS *(if any)*

LCS, NSB, NIMH

LAB/BRANCH

Clinical Neurogenetics Branch

SECTION

Section on Clinical Genetics

INSTITUTE AND LOCATION

NIMH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
8.8	4.5	4.3

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.)*

Family Studies. Controlled family studies of schizophrenia and bulimia are underway, with first reportable results expected during the coming year. In the affective disorders, we have identified a birth cohort effect on the prevalence of mania, such that in more recently born cohorts there are higher rates than in earlier born cohorts. These data are compatible with an ongoing increase in a spectrum of affective and related disorders, including mania, depression, and suicide.

Cell collections of transformed lymphocytes from pedigrees and affected sib-pairs with manic-depressive and schizophrenic illnesses are being constructed, for use in genetic linkage studies. Mathematical modelling has demonstrated the power of these methods for detection of single locus inheritance linked to a marker, given cell collections of the size we are collecting.

Receptors on peripheral cells. No differences in beta-receptor sensitivity or number in manic-depressive patients was found on fibroblasts or transformed lymphocytes. Other receptors for neuropeptides and smaller neurotransmitter molecules were carefully screened for, but were not present.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00084-12 CNG

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Genetic-Biologic Studies of Psychiatric Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.	E. Gershon	Chief	CNG, NIMH
Others:	L. DeLisi	Staff Psychiatrist	CNG, NIMH
	J.I. Nurnberger, Jr.	Medical Officer	CNG, NIMH
	W.H. Berrettini	Staff Psychiatrist	CNG, NIMH
	J. Hamovit	Research Social Worker	CNG, NIMH
	L. Goldin	Senior Staff Fellow	CNG, NIMH
	J. Baumgold	Research Chemist	CNG, NIMH

COOPERATING UNITS *(if any)*

LCS, NSB, NIMH

LAB/BRANCH

Clinical Neurogenetics Branch

SECTION

Section on Clinical Genetics

INSTITUTE AND LOCATION

NIMH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
8.8	4.5	4.3

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01-00085-10 CNG

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Pharmacogenetics of Psychoactive Drugs

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.	John I. Nurberger, Jr.	Medical Officer	CNG, NIMH
Others:	S. Simmons-Alling	Clinical Nurse Expert	CC, NIH
	W. Berrettini	Staff Psychiatrist	CNG, NIMH
	E. Gershon	Chief	CNG, NIMH
	D. Pickar	Section Chief	NSB, NIMH
	W. Mendelson	Section Chief	CPB, NIMH
	D. Sack	Medical Officer	CPB, NIMH

COOPERATING UNITS *(if any)*

CC, NIH; CPB, NIMH; NSB, NIMH

LAB/BRANCH

Clinical Neurogenetics Branch

SECTION

Section on Clinical Genetics

INSTITUTE AND LOCATION

NIMH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.9	1.1	.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.)*

Two biologic abnormalities reported during depression are excess production of cortisol and decreased latency to rapid-eye-movement (REM) sleep. We have attempted to provoke similar abnormalities in well state patients off medications.

The muscarinic cholinergic agonist arecoline has been used to induce REM in sleeping subjects. Our replication study has been completed and initial data analysis does not show a significant difference between 18 euthymic bipolar patients and 18 controls.

The serotonin precursor tryptophan and the opiate antagonist naloxone have been used to probe cortisol secretion. Dose-response studies have been completed. Both agents provoke significant increases in cortisol. Euthymic bipolar patient-control comparison of tryptophan responses do not show supersensitivity in patients.

The serotonin receptor blocker metergoline does not block the dextroamphetamine-induced rise in cortisol, although preliminary data did suggest this. A reanalysis of thymoxamine blockade of amphetamine suggests a possible role for alpha receptors in the cortisol response, at least in males.

Other Challenges: The calcium channel blocker diltiazem has been tested in 12 infusions to 7 persons in an ongoing study. Thirteen persons have received ACTH infusions as part of a study of steroid effects. Twelve persons have completed a study of clonidine effects on growth hormone.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01-00085-10 CNG

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

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PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.	John I. Nurberger, Jr.	Medical Officer	CNG, NIMH
Others:	S. Simmons-Alling	Clinical Nurse Expert	CC, NIH
	W. Berrettini	Staff Psychiatrist	CNG, NIMH
	E. Gershon	Chief	CNG, NIMH
	D. Pickar	Section Chief	NSB, NIMH
	W. Mendelson	Section Chief	CPB, NIMH
	D. Sack	Medical Officer	CPB, NIMH

COOPERATING UNITS *(if any)*

CC, NIH; CPB, NIMH; NSB, NIMH

LAB/BRANCH

Clinical Neurogenetics Branch

SECTION

Section on Clinical Genetics

INSTITUTE AND LOCATION

NIMH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.9	1.1	.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.)*

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00086-10 CNG

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Outpatient Clinic for Genetic and Pharmacological Studies of Affective Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.	J.I. Nurnberger, Jr.	Medical Officer	CNG, NIMH
Others:	L. DeLisi	Staff Psychiatrist	CNG, NIMH
	W. Berrettini	Staff Psychiatrist	CNG, NIMH
	E.S. Gershon, M.D.	Chief	CNG, NIMH
	S. Simmons-Alling	Clinical Nurse Expert	CC, NIH
	J.R. Hamovit	Research Social Worker	CNG, NIMH
	E. Maxwell	Social Worker	CNG, NIMH
	J. Johnson	Medical Student	Univ. Pittsburgh

COOPERATING UNITS *(if any)*

CC, NIH; CHP, BPB, LPP, LCS, NPB, LCS, NIMH; Catholic University; NSB, NIAAA, University of Pittsburgh

LAB/BRANCH

Clinical Neurogenetics Branch

SECTION

Section on Clinical Genetics

INSTITUTE AND LOCATION

NIMH, Bethesda, MD 20892

TOTAL MAN-YEARS:	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 high risk follow up study of offspring of bipolar (manic-depressive) parents is in its 3rd year. Five of 53 subjects have developed major affective disorder (as compared with 0/38 controls). The index subjects have increased scores on the disinhibition subscale of Zucherman's Sensation Seeking Scale.

We have completed a family study of rapid cycling bipolar patients. Relatives of rapid cyclers may have a lower morbid risk of major affective disorder. Initial data analysis suggests that non-genetic factors contribute to the etiology of this affective subtype.

Studies of CSF neuropeptides have continued. Neuropeptide Y levels were not altered in subjects with Alzheimer's disease, schizophrenia or eating disorders. Growth hormone releasing factor and atrial naturietic factor were not different in bipolar patients compared to controls. Sixteen neuropeptides, neurotransmitters and metabolites were measured in the same persons at different times and 14/16 were found to be stable.

Physostigmine infusions were done in an effort to provoke release of vaso-active intestinal polypeptide into CSF but this was not successful. Steroid treatment was found to lower cerebrospinal fluid beta endorphin and beta lipo-tropin.

Computerized tomographic scans have been measured to assess ventricular size in 59 bipolar subjects and 16 controls. Frontal horn measurements are not different in the two groups. Correlation of ventricular size with familial risk of affective illness and lithium response is continuing.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00086-10 CNG

PERIOD COVERED

October 1, 1985 to September 30, 1986

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P.I.	J.I. Nurnberger, Jr.	Medical Officer	CNG, NIMH
Others:	L. DeLisi	Staff Psychiatrist	CNG, NIMH
	W. Berrettini	Staff Psychiatrist	CNG, NIMH
	E.S. Gershon, M.D.	Chief	CNG, NIMH
	S. Simmons-Alling	Clinical Nurse Expert	CC, NIH
	J.R. Hamovit	Research Social Worker	CNG, NIMH
	E. Maxwell	Social Worker	CNG, NIMH
	J. Johnson	Medical Student	Univ. Pittsburgh

COOPERATING UNITS *(if any)*

CC, NIH; CHP, BPB, LPP, LCS, NPB, LCS, NIMH; Catholic University; NSB, NIAAA, University of Pittsburgh

LAB/BRANCH

Clinical Neurogenetics Branch

SECTION

Section on Clinical Genetics

INSTITUTE AND LOCATION

NIMH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.8	1.5	2.3

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02236-02 CNG

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Schizophrenia Studies

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.)* *(Name, title, laboratory, and institute affiliation)*

P.I.:	L.E. DeLisi	Staff Psychiatrist	CNG, NIMH
Others:	Elliot Gershon	Chief	CNG, NIMH
	S. Simmons-Alling	Clinical Nurse Expert	CC, NIH
	L.R. Goldin	Senior Staff Fellow	CNG, NIMH
	J.Nurnberger	Medical Officer	CNG, NIMH
	W. Berrettini	Staff Psychiatrist	CNG, NIMH
	C.W. Dingman	Staff Psychiatrist	Chestnut Lodge

COOPERATING UNITS *(if any)*

Springfield Hospital; Chestnut Lodge; Stanford; Laboratory for Cell Biology and Genetics, NIADDK, Clinical Center, NIH

LAB/BRANCH

Clinical Neurogenetics Branch

SECTION

Section on Clinical Genetics

INSTITUTE AND LOCATION

NIMH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.2	1.4	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.)*

Biological marker studies in schizophrenia:

1. Cytogenetic evaluations: No abnormal chromosomal patterns (including fragile-X) were noted in a study of approximately 40 males with schizophrenia.

2. Genetic Marker Studies: No association of Restriction Fragment Length Polymorphisms were found in genomic DNA from schizophrenics using Neuropeptide Y and somatotstatin DNA probes.

3. Viral studies (herpes class, HTLV antibodies) were negative. Although approximately 1/3 of schizophrenic patients studied had elevated antibody titres to Epstein-Barr virus (EBV), siblings with schizophrenia were not concordant for seropositivity, and a hospital control population was similarly increased. Treatment of these elevated EBV antibody titre patients with acyclovir did not produce beneficial effects.

4. Computed tomography (CT): The finding reported by others of an association of small heads with schizophrenia was not confirmed by our CT measurements.

Clinical study of schizophrenia sibs:

A study of clinical variables in multiplex families with schizophrenia is in progress. Over 60 families with more than one schizophrenic sibling have been recruited from throughout the USA, and clinical evaluations have been completed on all. Analysis of the data is in progress. Initial examination reveals no concordance for characteristic clinical symptoms, a negative symptom syndrome or for schizoaffective diagnoses within sets of siblings.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02236-02 CNG

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Schizophrenia Studies

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	L.E. DeLisi	Staff Psychiatrist	CNG, NIMH
Others:	Elliot Gershon	Chief	CNG, NIMH
	S. Simmons-Alling	Clinical Nurse Expert	CC, NIH
	L.R. Goldin	Senior Staff Fellow	CNG, NIMH
	J.Nurnberger	Medical Officer	CNG, NIMH
	W. Berrettini	Staff Psychiatrist	CNG, NIMH
	C.W. Dingman	Staff Psychiatrist	Chestnut Lodge

COOPERATING UNITS *(if any)*

Springfield Hospital; Chestnut Lodge; Stanford; Laboratory for Cell Biology and Genetics, NIADDK, Clinical Center, NIH

LAB/BRANCH

Clinical Neurogenetics Branch

SECTION

Section on Clinical Genetics

INSTITUTE AND LOCATION

NIMH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.2	1.4	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.)*

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02237-02 CNG

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Molecular Genetics of Neuropsychiatric Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	S. Detera-Wadleigh	Senior Staff Fellow	CNG, NIMH
Others:	E.S. Gershon	Chief	CNG, NIMH
	C. de Miguel	Visiting Fellow	CNG, NIMH
	Banani SenGupta	Guest Researcher	CNG, NIMH
	J.I. Nurnberger, Jr.	Medical Officer	CNG, NIMH
	W. Berrettini	Staff Psychiatrist	CNG, NIMH
	L. DeLisi	Staff Psychiatrist	CNG, NIMH
	L. Goldin	Senior Staff Fellow	CNG, NIMH

COOPERATING UNITS *(if any)*

Purdue University, New England Medical Center of Tufts University, Howard University, NINCDS, University of Cincinnati, Michigan State University

LAB/BRANCH

Clinical Neurogenetics Branch

SECTION

Section on Clinical Genetics

INSTITUTE AND LOCATION

NIMH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.2	2.3	1.9

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.)*

Restriction fragment length polymorphisms (RFLPs) were identified for the structural genes of neuropeptide Y (NPY), vasoactive intestinal peptide (VIP) and adenosine deaminase (ADA). Comparison of variant neuropeptide Y allele frequencies in both normal individuals and patients, that is, schizophrenics and manic-depressives show no significant difference. The linkage relationship between NPY and a putative major locus for manic-depressive illness was examined in two pedigrees. The lod scores obtained under various assumed modes of inheritance suggest absence of linkage.

Two restriction enzymes yielded RFLPs at the VIP locus and one enzyme revealed RFLPs in the region of the ADA gene. Association and linkage studies are being conducted using these probes.

A rat cDNA clone for calmodulin containing a 900 base pair (bp) insert was isolated from a rat brain λgt11 cDNA library. The cDNA was sequenced and found to encode the COOH terminal half of the calmodulin molecule, that is, residues 74-148. In this region of the molecule the rat, human and frog calmodulins are identical when the deduced rat sequence is used. The nucleotide homology in the coding region between rat and frog is 91% but only limited homology is observed in the 3' untranslated region. Human calmodulin cDNA was isolated from a gt10 cDNA library constructed using cytoplasmic RNA from NTeraD21 cell line. The insert encodes amino acid residues 10-148. The 3' untranslated region was highly homologous to the corresponding sequence in rat.

A neurotensin-specific cDNA clone was isolated from a rat brain gt11 cDNA library using a mixed oligonucleotide probe. The cDNA contains an 800 bp insert. Structural analysis of this DNA is now being done.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02237-02 CNG

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Molecular Genetics of Neuropsychiatric Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	S. Detera-Wadleigh	Senior Staff Fellow	CNG, NIMH
Others:	E.S. Gershon	Chief	CNG, NIMH
	C. de Miguel	Visiting Fellow	CNG, NIMH
	Banani SenGupta	Guest Researcher	CNG, NIMH
	J.I. Nurnberger, Jr.	Medical Officer	CNG, NIMH
	W. Berrettini	Staff Psychiatrist	CNG, NIMH
	L. DeLisi	Staff Psychiatrist	CNG, NIMH
	L. Goldin	Senior Staff Fellow	CNG, NIMH

COOPERATING UNITS *(if any)*

Purdue University, New England Medical Center of Tufts University, Howard University, NINCDS, University of Cincinnati, Michigan State University

LAB/BRANCH

Clinical Neurogenetics Branch

SECTION

Section on Clinical Genetics

INSTITUTE AND LOCATION

NIMH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.2	2.3	1.9

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.)*

Restriction fragment length polymorphisms (RFLPs) were identified for the structural genes of neuropeptide Y (NPY), vasoactive intestinal peptide (VIP) and adenosine deaminase (ADA). Comparison of variant neuropeptide Y allele frequencies in both normal individuals and patients, that is, schizophrenics and manic-depressives show no significant difference. The linkage relationship between NPY and a putative-major locus for manic-depressive illness was examined in two pedigrees. The lod scores obtained under various assumed modes of inheritance suggest absence of linkage.

Two restriction enzymes yielded RFLPs at the VIP locus and one enzyme revealed RFLPs in the region of the ADA gene. Association and linkage studies are being conducted using these probes.

A rat cDNA clone for calmodulin containing a 900 base pair (bp) insert was isolated from a rat brain λgt11 cDNA library. The cDNA was sequenced and found to encode the COOH terminal half of the calmodulin molecule, that is, residues 74-148. In this region of the molecule the rat, human and frog calmodulins are identical when the deduced rat sequence is used. The nucleotide homology in the coding region between rat and frog is 91% but only limited homology is observed in the 3' untranslated region. Human calmodulin cDNA was isolated from a gt10 cDNA library constructed using cytoplasmic RNA from NTeraD21 cell line. The insert encodes amino acid residues 10-148. The 3' untranslated region was highly homologous to the corresponding sequence in rat.

A neurotensin-specific cDNA clone was isolated from a rat brain gt11 cDNA library using a mixed oligonucleotide probe. The cDNA contains an 800 bp insert. Structural analysis of this DNA is now being done.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00935-19 CNG

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Studies of Plasmids and Small Genomes in Human Cells

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	C.R. Merril	Chief Biochemical Genetics Section	CNG NIMH
Others:	D. Rath	Staff Biologist	CNG NIMH
	M. Harrington	Visiting Associate	CNG NIMH
	S. Olson	Guest Scientist	CNG NIMH
	L. Mitchell	Staff Fellow	CNG NIMH
	L. Grossman	Senior Editor	Science Magazine
	B. Brown	Chief, Forensic Science Research	FBI Academy
	M. Kaiser	Ophthalmology	NEI

COOPERATING UNITS *(if any)*

NEI; Forensic Science Research Group, FBI Academy, Quantico, Virginia

LAB/BRANCH

Clinical Neurogenetics Branch

SECTION

Section on Biochemical Genetics

INSTITUTE AND LOCATION

NIMH, Bethesda, MD 20892

TOTAL MAN-YEARS:	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 scientific literature of a normally occurring plasmid genome, the mitochondrial genome, has indicated that the mutation rate of this closed circular DNA molecule is relatively high as compared to the nuclear or chromosomal genome. Taking this into consideration, studies are being conducted in collaboration with the FBI Forensic Science Research Group to determine whether these genetically inherited variations in the human mitochondrial genome are sufficient to establish ethnicity or even individuality for forensic applications.

Additionally, the clinical literature reveals a number of diseases that display non-Mendelian maternal inheritance patterns which may involve the mitochondrial genome. Using sequencing technologies, studies on the primary structure of mitochondrial DNA from normal individuals and from patients with maternally inherited diseases have been initiated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00935-19 CNG

PERIOD COVERED

October 1, 1985 to September 30, 1986

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PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	C.R. Merril	Chief Biochemical Genetics Section	CNG NIMH
Others:	D. Rath	Staff Biologist	CNG NIMH
	M. Harrington	Visiting Associate	CNG NIMH
	S. Olson	Guest Scientist	CNG NIMH
	L. Mitchell	Staff Fellow	CNG NIMH
	L. Grossman	Senior Editor	Science Magazine
	B. Brown	Chief, Forensic Science Research	FBI Academy
	M. Kaiser	Ophthalmology	NEI

COOPERATING UNITS *(if any)*

NEI; Forensic Science Research Group, FBI Academy, Quantico, Virginia

LAB/BRANCH

Clinical Neurogenetics Branch

SECTION

Section on Biochemical Genetics

INSTITUTE AND LOCATION

NIMH, Bethesda, MD 20892

TOTAL MAN-YEARS:	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 scientific literature of a normally occurring plasmid genome, the mitochondrial genome, has indicated that the mutation rate of this closed circular DNA molecule is relatively high as compared to the nuclear or chromosomal genome. Taking this into consideration, studies are being conducted in collaboration with the FBI Forensic Science Research Group to determine whether these genetically inherited variations in the human mitochondrial genome are sufficient to establish ethnicity or even individuality for forensic applications.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00941-06 CNG

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Biochemical Genetics and Metabolic Diseases

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.	C.R. Merril	Chief Biochemical Genetics Section	CNG, NIMH
Others:	M. Harrington	Visiting Associate	CNG, NIMH
	S. Olson	Guest Scientist	CNG, NIMH
	S. Charya	Visiting Fellows	CNG, NIMH

COOPERATING UNITS *(if any)* NIMH, NINCDS, Johns Hopkins Univ., NIAAA, St. Elizabeths Hosp., Univ. of Southern Ill., USUHS, NIH, Univ. of Detroit, Vanderbilt Univ., Harvard Medical School, Calif. Inst. of Tech., Univ. of Minn., Columbia Univ., Baylor College of Med., Univ. of Goteborg, UCLA

LAB/BRANCH

Clinical Neurogenetics Branch

SECTION

Section on Biochemical Genetics

INSTITUTE AND LOCATION

NIMH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
	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 2 CSF proteins (MW 26 and 29 k daltons) that were found previously in only Creutzfeldt-Jakob disease and Herpes simplex encephalitis, are absent from other causes of dementia (AIDS-associated dementia, multiinfart dementia, Alzheimer's disease, Huntington's disease, parkinsonism dementia of Guam) and other infections (tuberculous and syphilitic meningitis, and encephalitis from measles, cytomegalovirus, varicella, rubella, and three togaviruses.) Identification of these proteins in patients with dementia shows potential as a diagnostic test for Creutzfeldt-Jakob disease. Two proteins (both of 40 kd) that had been found in the spinal fluid of 30% of schizophrenic patients have been found in a small proportion (20%) of schizophrenics in an independent study, and results from two other populations are awaited.

One protein (25 kd) previously found in Parkinson's disease and MPTP-induced parkinsonism, has now been observed in a proportion of patients that have pathology common to the dopaminergic nigrostriatal neurones. Methods have been developed to obtain partial amino acid sequences of all 5 aforementioned disease-associated proteins and results are awaited.

The basic mechanism for the the visualization of protein and nucleic acids by silver staining has been shown to involve the reduction of ionic to metallic silver. Lysine and histidine, and the sulfur containing amino acids are the primary sites in the silver staining reactions. By utilizing sets of operationally constitutive proteins for the normalization of intra-gel stain intensities, quantitative comparisons of protein concentrations have been made in electrophoretograms from complex biological fluids or cellular extracts.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

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

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P.I.	C.R. Merril	Chief Biochemical Genetics Section	CNG, NIMH
Others:	M. Harrington	Visiting Associate	CNG, NIMH
	S. Olson	Guest Scientist	CNG, NIMH
	S. Charya	Visiting Fellows	CNG, NIMH

COOPERATING UNITS *(if any)* NIMH, NINCDS, Johns Hopkins Univ., NIAAA, St. Elizabeths Hosp., Univ. of Southern Ill., USUHS, NIH, Univ. of Detroit, Vanderbilt Univ., Harvard Medical School, Calif. Inst. of Tech., Univ. of Minn., Columbia Univ., Baylor College of Med., Univ. of Goteborg, UCLA

LAB/BRANCH

Clinical Neurogenetics Branch

SECTION

Section on Biochemical Genetics

INSTITUTE AND LOCATION

NIMH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
	3.5	

CHECK APPROPRIATE BOX(ES)

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02339-01 CNG

PERIOD COVERED

October 1, 1985 - September 30, 1986

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

Biochemistry and Pharmacology of Muscarinic and Other Neurotransmitter Receptors

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.	J. Baumgold	Research Chemist	CNG, NIMH
Others:	E. Gershon	Chief	CNG, NIMH
	C. Merril	Chief, Sect. on Biochemical Genetics	CNG, NIMH
	J. Avigan	Research Chemist	LCM, NHLBI
	P. Fishman	Chief, Sect. on Membrane Biochemistry	DMNB, NINCDS

COOPERATING UNITS *(if any)*

NINCDS, NHLBI

LAB/BRANCH

Clinical Neurogenetics Branch

SECTION

Section on Clinical Genetics

INSTITUTE AND LOCATION

NIMH, Bethesda, MD 20892

TOTAL MAN-YEARS:	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.)*

We have purified the muscarinic cholinergic receptor from bovine brain to near homogeneity, and have studied the binding of pirenzepine to this receptor at various stages of purification. In accord with previously published work, we found that in membrane-bound receptors, pirenzepine binds preferentially to receptors from cortex, compared to receptors from the pons/medulla. After digitonin solubilization, however, this difference is no longer detectable.

We have identified and characterized an endogenous muscarinic factor from acid-extracts of brain. This factor inhibits ligand binding to the muscarinic receptor and acts like an agonist in inhibiting prostaglandin-stimulated adenylate cyclase in NG108-15 neuroblastoma-glioma cells.

We found that the calcium channel inhibitor verapamil afects the binding characteristics of muscarinic receptors. These effects were studied in detail.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02339-01 CNG

PERIOD COVERED

October 1, 1985 - September 30, 1986

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P.I.	J. Baumgold	Research Chemist	CNG, NIMH
Others:	E. Gershon	Chief	CNG, NIMH
	C. Merril	Chief, Sect. on Biochemical Genetics	CNG, NIMH
	J. Avigan	Research Chemist	LCM, NHLBI
	P. Fishman	Chief, Sect. on Membrane Biochemistry	DMNB, NINCDS

COOPERATING UNITS *(if any)*

NINCDS, NHLBI

LAB/BRANCH

Clinical Neurogenetics Branch

SECTION

Section on Clinical Genetics

INSTITUTE AND LOCATION

NIMH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2	1	1

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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We found that the calcium channel inhibitor verapamil afects the binding characteristics of muscarinic receptors. These effects were studied in detail.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02242-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Consent Rates and Informed Consent in Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Llewellyn B. Bigelow, M.D., Associate Clinical Director for Research at Saint Elizabeths Hospital, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0	0	0

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 completed and terminated.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02242-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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Consent Rates and Informed Consent in Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Llewellyn B. Bigelow, M.D., Associate Clinical Director for Research at Saint Elizabeths Hospital, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	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 completed and terminated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02243-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Visual Hallucinations and the Visual Cortex in Patients with Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Haim Stefan Bracha, M.D., Medical Staff Fellow, NPB, IRP, NIMH

Dr. Jon Currie, National Eye Institute, NIH; Dr. Robert Wurtz, National Eye Institute, NIH; Dr. Craig N. Karson, Staff Psychiatrist, NPB, IRP, NIMH; Dr. Owen Wolkowitz, Section on Clinical Studies, Clinical Neurosciences Branch, NIMH; Dr. Fernando Cabrera, Saint Elizabeths Hospital; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

Saint Elizabeths Hospital; National Eye Institute, NIH; Section on Clinical Studies, Clinical Neurosciences Branch, NIMH

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Clinical Brain Studies

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital

TOTAL MAN-YEARS:	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.)*

We have examined lifetime prevalence of visual hallucinations in research subjects with schizophrenia in a retrospective study. We have found a lifetime prevalence of 32% and of those interviewed, 56%. Since it is commonly thought that visual hallucinations are more indicative of diseases of the brain other than schizophrenia, this study serves to dispel that notion and indicate another commonality between schizophrenia and some other diseases of the brain. Moreover, since these hallucinations are rare in mania, the presence of visual hallucinations in a patient may be a clue that the patient is suffering from schizophrenia.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02243-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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Haim Stefan Bracha, M.D., Medical Staff Fellow, NPB, IRP, NIMH

Dr. Jon Currie, National Eye Institute, NIH; Dr. Robert Wurtz, National Eye Institute, NIH; Dr. Craig N. Karson, Staff Psychiatrist, NPB, IRP, NIMH; Dr. Owen Wolkowitz, Section on Clinical Studies, Clinical Neurosciences Branch, NIMH; Dr. Fernando Cabrera, Saint Elizabeths Hospital; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

Saint Elizabeths Hospital; National Eye Institute, NIH; Section on Clinical Studies, Clinical Neurosciences Branch, NIMH

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Clinical Brain Studies

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital

TOTAL MAN-YEARS:	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.)*

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02244-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Behavioral Effects of Neurotoxic Substances and Their Neurochemical Correlates

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Jean Lud Cadet, M.D., Medical Staff Fellow, Section on Clinical Neuropsychiatry, NPB, IRP, NIMH

Dr. William J. Freed, Chief, Preclinical Neurosciences Section, NPB, IRP, NIMH; Dr. Richard Rothman, Guest Worker, Laboratory of Preclinical Pharmacology, IRP, NIMH; Dr. De-Maw Chuang, Laboratory of Preclinical Pharmacology, IRP, NIMH; Dr. Michael Iadorala, Staff Fellow, National Institute of Dental Research; Dr. Anthony Adinolfi, University of California, Los Angeles, California

COOPERATING UNITS *(if any)*

National Institute of Dental Research (NIDR); University of California, Los Angeles, California

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Clinical Neuropsychiatry

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	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.)*

We are continuing to study the toxic effect of various substances on the behavior of rodents. Several pharmacological studies and biochemical studies have been completed. Some have been presented at scientific meetings and are being written and will be submitted soon. Histological studies are in progress.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02244-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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Dr. William J. Freed, Chief, Preclinical Neurosciences Section, NPB, IRP, NIMH; Dr. Richard Rothman, Guest Worker, Laboratory of Preclinical Pharmacology, IRP, NIMH; Dr. De-Maw Chuang, Laboratory of Preclinical Pharmacology, IRP, NIMH; Dr. Michael Iadorala, Staff Fellow, National Institute of Dental Research; Dr. Anthony Adinolfi, University of California, Los Angeles, California

COOPERATING UNITS *(if any)*

National Institute of Dental Research (NIDR); University of California, Los Angeles, California

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Clinical Neuropsychiatry

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	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.)*

We are continuing to study the toxic effect of various substances on the behavior of rodents. Several pharmacological studies and biochemical studies have been completed. Some have been presented at scientific meetings and are being written and will be submitted soon. Histological studies are in progress.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02245-02 NPB

PERIOD COVERED
October 1, 1985 through September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Functional Consequences of Experimental Nerve Lesions

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
Luis de Medinaceli, M.D., Visiting Scientist, Neuropsychiatry Branch, IRP, NIMH

Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH
Neuropsychiatry Branch

SECTION
Section on Aging

INSTITUTE AND LOCATION
NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	.5	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.)*

Crush lesions were made on sciatic nerves of rats. We examined the influence on recovery of the time elapsed between successive injuries and of location and number of damaged sites. The results were assessed over a post-operative period of 2.5 months by studying tracks obtained from walking rats. This study demonstrated the capital role of basal lamina tube lesions in nerve injuries. In contrast, neither injury to the tissue of the nerve (Schwann cells), nor to the neurite itself influenced the functional outcome.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02245-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

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PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Luis de Medinaceli, M.D., Visiting Scientist, Neuropsychiatry Branch, IRP, NIMH

Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Aging

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	.5	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.)*

Crush lesions were made on sciatic nerves of rats. We examined the influence on recovery of the time elapsed between successive injuries and of location and number of damaged sites. The results were assessed over a post-operative period of 2.5 months by studying tracks obtained from walking rats. This study demonstrated the capital role of basal lamina tube lesions in nerve injuries. In contrast, neither injury to the tissue of the nerve (Schwann cells), nor to the neurite itself influenced the functional outcome.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02246-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Post-Traumatic Autoimmune Reaction In Peripheral Nerve

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Luis de Medinaceli, M.D., Visiting Scientist, Neuropsychiatry Branch, IRP, NIMH

Dr. Yen-Nung Wang, Visiting Associate, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Aging

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.25	.25	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 conducted to show whether local autoimmune reactions can be observed after injury to the sciatic nerve in the rat. Furthermore, we attempted to correlate the intensity of the immunological reaction with the severity of nerve damage, the type of surgical treatment and the degree of functional recovery. A direct influence of autoimmunization was found. Its effect on functional recovery was moderate but constant.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02246-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Post-Traumatic Autoimmune Reaction In Peripheral Nerve

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Luis de Medinaceli, M.D., Visiting Scientist, Neuropsychiatry Branch, IRP, NIMH

Dr. Yen-Nung Wang, Visiting Associate, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Aging

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.25	.25	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 conducted to show whether local autoimmune reactions can be observed after injury to the sciatic nerve in the rat. Furthermore, we attempted to correlate the intensity of the immunological reaction with the severity of nerve damage, the type of surgical treatment and the degree of functional recovery. A direct influence of autoimmunization was found. Its effect on functional recovery was moderate but constant.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02247-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Prediction of Outcome of Peripheral Nerve Injuries - A Probability Model

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Luis de Medinaceli, M.D., Visiting Scientist, Neuropsychiatry Branch, IRP, NIMH

Dr. Robert R. Rawlings, Mathematical Statistician, Division of Biometry and Epidemilogy, NIAAA; Dr. Yen-Nung Wang, Visiting Associate, Neuropsychiatry Branch, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

Division of Biometry and Epidemiology, NIAAA

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Aging

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.25	.25	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 long term functional consequences of peripheral nerve injuries are notoriously unpredictable. We hypothesized that considering the individual regrowth of the elementary components of a nerve (the neurites) rather than the global regeneration of the organ could lead to a better understanding of the mechanisms of nerve repair.

We postulated that the regrowth of any individual neurite can be defined in terms of its influence on recovery, the three main possibilities being valid, neutral and invalid regrowth. We have designed a probability model describing the prospects of regrowth for nerve composed of several types of fibers. This model is being tested in pre-determined situations to judge its validity. We found that possible variations in the outcome of nerve injuries could be explained by a parsimonious hypothesis: the randomness of regrowth.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02247-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Prediction of Outcome of Peripheral Nerve Injuries - A Probability Model

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Luis de Medinaceli, M.D., Visiting Scientist, Neuropsychiatry Branch, IRP, NIMH

Dr. Robert R. Rawlings, Mathematical Statistician, Division of Biometry and Epidemilogy, NIAAA; Dr. Yen-Nung Wang, Visiting Associate, Neuropsychiatry Branch, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

Division of Biometry and Epidemiology, NIAAA

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Aging

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.25	.25	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 long term functional consequences of peripheral nerve injuries are notoriously unpredictable. We hypothesized that considering the individual regrowth of the elementary components of a nerve (the neurites) rather than the global regeneration of the organ could lead to a better understanding of the mechanisms of nerve repair.

We postulated that the regrowth of any individual neurite can be defined in terms of its influence on recovery, the three main possibilities being valid, neutral and invalid regrowth. We have designed a probability model describing the prospects of regrowth for nerve composed of several types of fibers. This model is being tested in pre-determined situations to judge its validity. We found that possible variations in the outcome of nerve injuries could be explained by a parsimonious hypothesis: the randomness of regrowth.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02248-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Endogenous Substance Extract from Human Brain Inhibiting Neuroleptic Binding

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Anne-Marie Duchemin, M.D., Visiting Fellow, NPB, IRP, NIMH

Dr. Bruce H. Phelps, Staff Fellow, NPB, IRP, NIMH; Dr. C. David Wise, Research Chemist, NPB, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	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 has been terminated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02248-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

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PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Anne-Marie Duchemin, M.D., Visiting Fellow, NPB, IRP, NIMH

Dr. Bruce H. Phelps, Staff Fellow, NPB, IRP, NIMH; Dr. C. David Wise, Research Chemist, NPB, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	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 has been terminated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02249-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Ontogeny of Preprocholecystokinin mRNA and Cholecystokinin in the Rat Brain

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Anne-Marie Duchemin, M.D., Visiting Fellow, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	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 is continued under number Z01 MH 02311-01 NPB

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02249-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Ontogeny of Preprocholecystokinin mRNA and Cholecystokinin in the Rat Brain

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Anne-Marie Duchemin, M.D., Visiting Fellow, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	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 is continued under number Z01 MH 02311-01 NPB

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02250-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Purification of Messenger RNAs Encoding for Neurotrophic Factors in the Rat Brain

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Anne-Marie Duchemin, M.D., Visiting Fellow, Neuropsychiatry Branch, IRP, NIMH

Dr. Thanh Than Quach, Guest Worker, Neuropsychiatry Branch, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH; Dr. Bruce K. Schrier, Laboratory of Developmental Neurobiology, NICHD, NIH

COOPERATING UNITS *(if any)*

Laboratory of Developmental Neurobiology, NICHD, NIH

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Officer of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.33	.33	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.)*

Neurotrophic factors have been shown to appear in the cat brain after lesion. This project intends the molecular cloning of the gene encoding for these lesion-induced trophic factors in the brain.

During 1985, we developed the assays to produce these factors and test for their neurotrophic activity. A fraction of mRNA, prepared from lesioned rat brain, responsible for neurotrophic activity was found by in vivo translation into proteins in Xenopus Laevis oocytes.

During the last past months, we constructed a cDNA library specific for lesioned rat brain in the Bluescribe MB vector. The selection of the positive clones and the sequencing of the corresponding gene is in progress.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02250-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

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PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Anne-Marie Duchemin, M.D., Visiting Fellow, Neuropsychiatry Branch, IRP, NIMH

Dr. Thanh Than Quach, Guest Worker, Neuropsychiatry Branch, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH; Dr. Bruce K. Schrier, Laboratory of Developmental Neurobiology, NICHD, NIH

COOPERATING UNITS *(if any)*

Laboratory of Developmental Neurobiology, NICHD, NIH

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Officer of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.33	.33	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.)*

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During the last past months, we constructed a cDNA library specific for lesioned rat brain in the Bluescribe MB vector. The selection of the positive clones and the sequencing of the corresponding gene is in progress.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02251-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Distribution of Brain Somatostatin mRNA

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Anita Feenstra, Ph.D., Visiting Associate, NPB, IRP, NIMH

Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.5	.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.)*

We have initiated a study of the local distribution of somatostatin mRNA in brains of patients with schizophrenia and Huntington's disease. The mRNA extraction method was adopted for brain tissue. Brains of patients and normal brains are being collected, and the proper area's are dissected.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02251-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Distribution of Brain Somatostatin mRNA

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Anita Feenstra, Ph.D., Visiting Associate, NPB, IRP, NIMH

Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.5	.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.)*

We have initiated a study of the local distribution of somatostatin mRNA in brains of patients with schizophrenia and Huntington's disease. The mRNA extraction method was adopted for brain tissue. Brains of patients and normal brains are being collected, and the proper area's are dissected.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02252-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Behavioral Pharmacology and Toxicology

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

William J. Freed, Ph.D., Chief, Preclinical Neurosciences Section, NPB, IRP, NIMH

Dr. Renaud de Beaurepaire, Visiting Associate, NPB, IRP, NIMH; Dr. Jack A. Grebb, Laboratory of Molecular and Cellular Neuroscience, Rockfeller University, New York; Dr. Richard Shelton, Department of Psychiatry, Vanderbilt University School of Medicine, Nashville, Tenn.; Dr. Saul Schwartz, Department of Neurosurgery, Naval Medical Center, Bethesda, Maryland

COOPERATING UNITS *(if any)*

Vanderbilt University School of Medicine, Nashville, Tenn.
Department of Neurosurgery, Naval Medical Center, Bethesda, Maryland
Laboratory of Molecular and Cellular, Rockfeller University, New York

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Preclinical Neurosciences Section

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2	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.)*

The project on behavioral pharmacology and toxicology is derived from an ongoing interest in brain function, from the presumption that schizophrenia is a disease of the brain and from a belief that behavioral studies can be windows on in vivo processes. The studies continued through this past reporting year have yielded a series of interesting results suggesting new directions for future research.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02252-02 NPB

PERIOD COVERED
October 1, 1985 through September 30, 1986

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

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
William J. Freed, Ph.D., Chief, Preclinical Neurosciences Section, NPB, IRP, NIMH

Dr. Renaud de Beaurepaire, Visiting Associate, NPB, IRP, NIMH; Dr. Jack A. Grebb, Laboratory of Molecular and Cellular Neuroscience, Rockfeller University, New York; Dr. Richard Shelton, Department of Psychiatry, Vanderbilt University School of Medicine, Nashville, Tenn.; Dr. Saul Schwartz, Department of Neurosurgery, Naval Medical Center, Bethesda, Maryland

COOPERATING UNITS *(if any)*
Vanderbilt University School of Medicine, Nashville, Tenn.
Department of Neurosurgery, Naval Medical Center, Bethesda, Maryland
Laboratory of Molecular and Cellular, Rockfeller University, New York

LAB/BRANCH
Neuropsychiatry Branch

SECTION
Preclinical Neurosciences Section

INSTITUTE AND LOCATION
NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2	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.)*

The project on behavioral pharmacology and toxicology is derived from an ongoing interest in brain function, from the presumption that schizophrenia is a disease of the brain and from a belief that behavioral studies can be windows on in vivo processes. The studies continued through this past reporting year have yielded a series of interesting results suggesting new directions for future research.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02253-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Brain Tissue Transplantation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

William J. Freed, Ph.D., Chief, Preclinical Neurosciences Section, NPB, IRP, NIMH

Dr. Urmi Patel-Vaidya, Staff Fellow, NPB, IRP, NIMH; Renaud de Beaurepaire, Visiting Associate, NPB, IRP, NIMH; Dr. Herbert Geller, Rutgers University, New Brunswick, New Jersey; Dr. Jeff Laskin of Rutgers University, New Brunswick, New Jersey; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

Rutgers University, New Jersey; Naval Medical Center, Bethesda, Maryland; University of Minnesota; University of Michigan

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Preclinical Neurosciences Section

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	.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.)*

These studies of brain tissue transplantation in non-primate animals attempt (1) to develop the techniques of brain tissue transplantation so that it may be applied clinically to Parkinson's disease. (2) To develop brain tissue transplantation techniques for eventual application to other disorders, such as schizophrenia or Alzheimer's disease if and when these disorders become well enough understood to permit such applications, and (3) to employ brain tissue transplantation as a technique to elucidate factors that control the development and plasticity of the brain, particularly the nigrostriatal dopamine system. During the past reporting year important progress has been made toward achieving these goals.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02253-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Brain Tissue Transplantation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

William J. Freed, Ph.D., Chief, Preclinical Neurosciences Section, NPB, IRP, NIMH

Dr. Urmi Patel-Vaidya, Staff Fellow, NPB, IRP, NIMH; Renaud de Beaurepaire, Visiting Associate, NPB, IRP, NIMH; Dr. Herbert Geller, Rutgers University, New Brunswick, New Jersey; Dr. Jeff Laskin of Rutgers University, New Brunswick, New Jersey; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

Rutgers University, New Jersey; Naval Medical Center, Bethesda, Maryland; University of Minnesota; University of Michigan

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Preclinical Neurosciences Section

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	.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.)*

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02254-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Calcium Channel Inhibitors: Interactions with Dopaminergic Systems - Animal Studies

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Jack A. Grebb, M.D., Medical Staff Associate, NPB, NIMH

Dr. Richard C. Shelton, Medical Staff Associate, NPB, NIMH; Dr. Jean L. Cadet, Medical Staff Associate, NPB, NIMH; Dr. William J. Freed, Chief, Preclinical Neurosciences Section, NPB, NIMH; Dr. Gabriele Panza, Visiting Associate, Section on Biochemical Pharmacology, NHLBI, NIMH; Dr. Ingeborg Hanbauer, Section on Biochemical Pharmacology, NHLBI; NIMH

COOPERATING UNITS *(if any)*

Section on Biochemical Pharmacology, NHLBI

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	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 because the investigator left NIMH.

GPO 914-916

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02254-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Calcium Channel Inhibitors: Interactions with Dopaminergic Systems - Animal Studies

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Jack A. Grebb, M.D., Medical Staff Associate, NPB, NIMH

Dr. Richard C. Shelton, Medical Staff Associate, NPB, NIMH; Dr. Jean L. Cadet, Medical Staff Associate, NPB, NIMH; Dr. William J. Freed, Chief, Preclinical Neurosciences Section, NPB, NIMH; Dr. Gabriele Panza, Visiting Associate, Section on Biochemical Pharmacology, NHLBI, NIMH; Dr. Ingeborg Hanbauer, Section on Biochemical Pharmacology, NHLBI; NIMH

COOPERATING UNITS *(if any)*

Section on Biochemical Pharmacology, NHLBI

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	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 because the investigator left NIMH.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02255-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Calcium Channel Inhibitors: Interactions Systems - Human Studies

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Gregory M. Straw, M.D., Medical Staff Fellow, Neuropsychiatry Branch, IRP, NIMH

Dr. Darrell Kirch, Senior Staff Fellow, NPB, IRP, NIMH; Dr. Llewellyn B. Bigelow, Associate Clinical Director for WAW Division, Saint Elizabeths Hospital; Dr. Edward Taylor, Clinical Social Worker, WAW Division, Saint Elizabeths Hospital

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Preclinical Neurosciences Section

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	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.)*

Calcium channel inhibitors (CCI's) are thought to affect calcium flux through membrane bound channels as their major site of action. There are reports of clinical trials involving over 150 patients suggesting that CCI's also have beneficial effects in neuropsychiatric disorders. There are four major subclasses of CCI's, where each appears to have unique combinations of biochemical and behavioral properties. Additional studies have suggested a complex interaction between dopamine receptor function and calcium channels. We have completed a study of the clinical effects of verapamil in a schizophrenic population where trends toward improvement did not reach statistical significance. We are proceeding with the planned protocol to examine the effects of nifedipine in a similar cohort. Different results are to be expected on the basis of preliminary work where nifedipine differed from verapamil its effects on animal behavior in models of dopaminergic activity.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02255-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Calcium Channel Inhibitors: Interactions Systems - Human Studies

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Gregory M. Straw, M.D., Medical Staff Fellow, Neuropsychiatry Branch, IRP, NIMH

Dr. Darrell Kirch, Senior Staff Fellow, NPB, IRP, NIMH; Dr. Llewellyn B. Bigelow, Associate Clinical Director for WAW Division, Saint Elizabeths Hospital; Dr. Edward Taylor, Clinical Social Worker, WAW Division, Saint Elizabeths Hospital

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Preclinical Neurosciences Section

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	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.)*

Calcium channel inhibitors (CCI's) are thought to affect calcium flux through membrane bound channels as their major site of action. There are reports of clinical trials involving over 150 patients suggesting that CCI's also have beneficial effects in neuropsychiatric disorders. There are four major subclasses of CCI's, where each appears to have unique combinations of biochemical and behavioral properties. Additional studies have suggested a complex interaction between dopamine receptor function and calcium channels. We have completed a study of the clinical effects of verapamil in a schizophrenic population where trends toward improvement did not reach statistical significance. We are proceeding with the planned protocol to examine the effects of nifedipine in a similar cohort. Different results are to be expected on the basis of preliminary work where nifedipine differed from verapamil its effects on animal behavior in models of dopaminergic activity.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02256-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Defect Symptoms in Schizophrenia: Their Measurement, Correlates and Treatment

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dr. Darrell G. Kirch, Senior Staff Fellow, NPB, IRP, NIMH

Dr. Edward H. Taylor, Clinical Social Worker, WAW Division, Saint Elizabeths Hospital; Dr. Irene Namyslowska, Visiting Psychiatrist, WAW Division, Saint Elizabeths Hospital; Dr. Joel E. Kleinman, Chief, Section on Clinical Brain Studies, NPB, IRP, NIMH; Dr. Llewellyn B. Bigelow, Associate Clinical Director of WAW Division, NIMH; Dr. Craig N. Karson, Acting Chief, Section on Clinical Brain Studies, NPB, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH; Dr. Terry Goldberg, Special Expert, Section on Clinical Psychiatry, NPB, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Psychopharmacology

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.5	.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.)*

Renewed interest in the role of negative symptoms in "defect state" schizophrenia encouraged us to develop a "Negative Symptom Rating Scale (NSRS)" to more efficiently measure this syndrome.

This study explores the relationship between schizophrenia, social intelligence, general intelligence, negative symptoms and premorbid social functioning in schizophrenic patients.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02256-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

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PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dr. Darrell G. Kirch, Senior Staff Fellow, NPB, IRP, NIMH

Dr. Edward H. Taylor, Clinical Social Worker, WAW Division, Saint Elizabeths Hospital; Dr. Irene Namyslowska, Visiting Psychiatrist, WAW Division, Saint Elizabeths Hospital; Dr. Joel E. Kleinman, Chief, Section on Clinical Brain Studies, NPB, IRP, NIMH; Dr. Llewellyn B. Bigelow, Associate Clinical Director of WAW Division, NIMH; Dr. Craig N. Karson, Acting Chief, Section on Clinical Brain Studies, NPB, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH; Dr. Terry Goldberg, Special Expert, Section on Clinical Psychiatry, NPB, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Psychopharmacology

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.5	.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.)*

Renewed interest in the role of negative symptoms in "defect state" schizophrenia encouraged us to develop a "Negative Symptom Rating Scale (NSRS)" to more efficiently measure this syndrome.

This study explores the relationship between schizophrenia, social intelligence, general intelligence, negative symptoms and premorbid social functioning in schizophrenic patients.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02257-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Biochemical and Neuroradiologic Abnormalities in Tardive Dyskinesia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

James B. Lohr, M.D., Medical Staff Fellow, Neuropsychiatry Branch, NIMH

Dr. Dilip V. Jeste, Staff Psychiatrist, NPB, IRP, NIMH; Dr. Jean L. Cadet, Medical Staff Fellow, NPB, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH; Dr. Evelyn Wasli, NRAB, St. Elizabeths Hospital; Dr. Elaine Apostoles, St. Elizabeths Hospital

COOPERATING UNITS *(if any)*

Nursing Research Advisory Board, Saint Elizabeths Hospital

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Aging

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.5	.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.)*

We have been studying the efficacy of antioxidant therapy for tardive dyskinesia (TD). The treatments involve alpha-tocopherol and d-penicillamine. Preliminary results reveal a significant improvement in movement disorder and a trend toward improvement in psychopathology in schizophrenic and schizoaffective patients with TD after administration of alpha-tocopherol, but no change in parkinsonism with this agent.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02257-02 NPB

PERIOD COVERED
October 1, 1985 through September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Biochemical and Neuroradiologic Abnormalities in Tardive Dyskinesia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
James B. Lohr, M.D., Medical Staff Fellow, Neuropsychiatry Branch, NIMH

Dr. Dilip V. Jeste, Staff Psychiatrist, NPB, IRP, NIMH; Dr. Jean L. Cadet, Medical Staff Fellow, NPB, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH; Dr. Evelyn Wasli, NRAB, St. Elizabeths Hospital; Dr. Elaine Apostoles, St. Elizabeths Hospital

COOPERATING UNITS *(if any)*
Nursing Research Advisory Board, Saint Elizabeths Hospital

LAB/BRANCH
Neuropsychiatry Branch

SECTION
Section on Aging

INSTITUTE AND LOCATION
NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.5	.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.)*

We have been studying the efficacy of antioxidant therapy for tardive dyskinesia (TD). The treatments involve alpha-tocopherol and d-penicillamine. Preliminary results reveal a significant improvement in movement disorder and a trend toward improvement in psychopathology in schizophrenic and schizoaffective patients with TD after administration of alpha-tocopherol, but no change in parkinsonism with this agent.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02258-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Quantitative Neuropathology of Aging and Neuropsychiatric Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dr. Dilip V. Jeste, Special Expert, Neuropsychiatry Branch, IRP, NIMH

Dr. James B. Lohr, Medical Staff Fellow, NPB, IRP, NIMH; Dr. Carol Ludwig, Department of Neurology, George Washington University Hospital, Washington, D.C.; Dr. Joseph Parisi, Chairman, Department of Neuropathology, Armed Forces Institute of Pathology, Bethesda, Maryland; Dr. Francine Benes, Department of Psychiatry, McLean Research Center, Boston, MA.

COOPERATING UNITS *(if any)*

Department of Neurology, George Washington University Hospital, Washington, D.C.; Department of Neuropathology, Armed Forces Institute of Pathology, Bethesda, Maryland; Department of Psychiatry, McLean Research Center, Boston, MA.

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Aging

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.5	.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.)*

We have been studying quantitative volume, neuronal density, neuronal size and nuclear size in selected areas of brains from patients with certain neuropsychiatric disorders as well as normal controls from different age groups. Results to date indicate that there is normally age-related Purkinje cell loss in the cerebellum, pyramidal cell loss in area CA4 of the hippocampus, and neuron loss in the locus ceruleus. In schizophrenic subjects, we found a significant decrease in the pyramidal cell density in area CA4 of the hippocampus, mainly in the left hemisphere when compared to controls, and a trend toward a reduction in CA4 density in affective disorder patients as well. We found no significant morphological differences between schizophrenic patients, affective disorder patients and normal controls in cerebellum or locus ceruleus.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02258-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Quantitative Neuropathology of Aging and Neuropsychiatric Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dr. Dilip V. Jeste, Special Expert, Neuropsychiatry Branch, IRP, NIMH

Dr. James B. Lohr, Medical Staff Fellow, NPB, IRP, NIMH; Dr. Carol Ludwig, Department of Neurology, George Washington University Hospital, Washington, D.C.; Dr. Joseph Parisi, Chairman, Department of Neuropathology, Armed Forces Institute of Pathology, Bethesda, Maryland; Dr. Francine Benes, Department of Psychiatry, McLean Research Center, Boston, MA.

COOPERATING UNITS *(if any)*

Department of Neurology, George Washington University Hospital, Washington, D.C.; Department of Neuropathology, Armed Forces Institute of Pathology, Bethesda, Maryland; Department of Psychiatry, McLean Research Center, Boston, MA.

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Aging

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.5	.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.)*

We have been studying quantitative volume, neuronal density, neuronal size and nuclear size in selected areas of brains from patients with certain neuropsychiatric disorders as well as normal controls from different age groups. Results to date indicate that there is normally age-related Purkinje cell loss in the cerebellum, pyramidal cell loss in area CA4 of the hippocampus, and neuron loss in the locus ceruleus. In schizophrenic subjects, we found a significant decrease in the pyramidal cell density in area CA4 of the hippocampus, mainly in the left hemisphere when compared to controls, and a trend toward a reduction in CA4 density in affective disorder patients as well. We found no significant morphological differences between schizophrenic patients, affective disorder patients and normal controls in cerebellum or locus ceruleus.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02259-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Peripheral and Central Catecholamine Turnover in Depression and Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Farouk Karoum, Ph.D., Chemist, Neuropsychiatry Branch, IRP, NIMH

Dr. Esa Korpi, Research Laboratories, Helsinki, Finland; Dr. Craig N. Karson, Staff Psychiatrist, NPB, IRP, NIMH; Dr. William B. Lawson, Faculty Member, University of California, Irvine, California; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH; Dr. Markku Linnoila, LCS, DICBR, NIAAA; Dr. Alan J. Zametkin, Laboratory of Clinical Science, IRP, NIMH

COOPERATING UNITS *(if any)*

Research Laboratories, Helsinki, Finland; University of California, Irvine, California, Laboratory of Clinical Studies, NIAAA; Laboratory of Clinical Sciences, NIMH

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Psychopharmacology

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	.5	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.)*

Combined gas chromatographic mass spectrometric methods previously developed for the assay of biogenic amines in various biological media have been employed to assess total body turnover of norepinephrine (sum NE) and dopamine (sum DA) in both human subjects and rats. We have also compared changes in sum NE and sum DA after a number of pharmacological manimpulations in rats. The aim of these animal studies was to gain an insight into how these pharmacological treatments influence brain catecholamines in depression, schizophrenia and hyperactive children.

(1) Consistent with our 1985 Annual Report, we have continued to gather additional supportive data that suggest a tendency for sum NE to be elevated in major depression.

(2) Preliminary results sited in 1985 Annual Report on sum NE and sum DA in schizophrenia were substantiated.

(3) Total body NE and DA turnover were assessed in both hyperactive children and adults after a number of pharmacological manipulations. The results indicated a correlation between therapeutic benefit and changes in both sum NE and DA irrespective of the direction of change.

(4) The effects of four commonly used antidepressant treatments on rat peripheral and central catecholamines were evaluated. A good correlation between the effects of these drugs and sum NE and sum DA in humans and rats was observed. It is suggested that because of this correlation, changes in the rat brain amines observed probably resemble the changes these treatments induce in the human brain. The four treatments employed were chronic zimelidine, desipramine, electroconvulsion and lithium.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02259-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Peripheral and Central Catecholamine Turnover in Depression and Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Farouk Karoum, Ph.D., Chemist, Neuropsychiatry Branch, IRP, NIMH

Dr. Esa Korpi, Research Laboratories, Helsinki, Finland; Dr. Craig N. Karson, Staff Psychiatrist, NPB, IRP, NIMH; Dr. William B. Lawson, Faculty Member, University of California, Irvine, California; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH; Dr. Markku Linnoila, LCS, DICBR, NIAAA; Dr. Alan J. Zametkin, Laboratory of Clinical Science, IRP, NIMH

COOPERATING UNITS *(if any)*

Research Laboratories, Helsinki, Finland; University of California, Irvine, California, Laboratory of Clinical Studies, NIAAA; Laboratory of Clinical Sciences, NIMH

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Psychopharmacology

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	.5	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.)*

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02261-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Clinical Phenomena in Schizophrenia: Quantification in an Effort to Subtype

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dr. Craig N. Karson, Staff Psychiatrist, NPB, IRP, NIMH

Dr. Llewellyn B. Bigelow, Associate Clinical Director, WAW Division, Saint Elizabeths Hospital, NIMH; Dr. Darrell G. Kirch, Senior Staff Fellow, NPB, DIRP, NIMH; Dr. Joel E. Kleinman, Chief, Section on Clinical Brain Studies, NPB, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Clinical Neuropsychiatry

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.5	.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.)*

Despite wide variations in the clinical manifestations of schizophrenia, it remains difficult for clinicians to design novel treatments or predict vulverability to negative outcomes (including medication side effects) based on signs and symptoms of the disorder. By focusing on certain clinical characteristics of schizophrenia we have designed a series of experimental medication treatments. This involves the notion that the disorder is associated with impaired cognitive performance. Hence, we have begun trials of medication that may improve cognition. Our first such trial utilized DDAVP with at least modest success.

In addition we have looked for clinical manifestations potentially associated with poor outcomes. We have found that patients with schizophrenia are more assaultive than other seriously ill psychiatric patients while in the hospital and that a previous history of assaultive is associated with an increase number of hospitalizations. With regards to the major side effect of neuroleptic treatment, tardive dyskinesia (TD), we have found that depression may be associated with a more severe variant.

- DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02261-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Clinical Phenomena in Schizophrenia: Quantification in an Effort to Subtype

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dr. Craig N. Karson, Staff Psychiatrist, NPB, IRP, NIMH

Dr. Llewellyn B. Bigelow, Associate Clinical Director, WAW Division, Saint Elizabeths Hospital, NIMH; Dr. Darrell G. Kirch, Senior Staff Fellow, NPB, DIRP, NIMH; Dr. Joel E. Kleinman, Chief, Section on Clinical Brain Studies, NPB, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Clinical Neuropsychiatry

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.5	.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.)*

Despite wide variations in the clinical manifestations of schizophrenia, it remains difficult for clinicians to design novel treatments or predict vulnerability to negative outcomes (including medication side effects) based on signs and symptoms of the disorder. By focusing on certain clinical characteristics of schizophrenia we have designed a series of experimental medication treatments. This involves the notion that the disorder is associated with impaired cognitive performance. Hence, we have begun trials of medication that may improve cognition. Our first such trial utilized DDAVP with at least modest success.

In addition we have looked for clinical manifestations potentially associated with poor outcomes. We have found that patients with schizophrenia are more assaultive than other seriously ill psychiatric patients while in the hospital and that a previous history of assaultive is associated with an increase number of hospitalizations. With regards to the major side effect of neuroleptic treatment, tardive dyskinesia (TD), we have found that depression may be associated with a more severe variant.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02262-02 NPB

PERIOD COVERED

October 1, 1985 through September 30,1986

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

Electroretinography in Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Myles J. Jaffe, O.D., Senior Staff Fellow, Neuropsychiatry Branch, IRP, NIMH

Dr. Craig N. Karson, Staff Psychiatrist, Section on Clinical Neuropsychiatry, NPB, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	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.)*

The ganzfeld electroretinogram has revealed that both dopaminergic blockers and GABA potentiators have an inhibitory effect on human rods and cones. In a related clinical study, we have repeatedly shown the blue-sensitive cone system to be altered in male drug-free patients with schizophrenia when compared with age- and sex-matched controls. These results suggest that the neuromodulators of the retina may be altered by psychoactive drugs and psychiatric disease in a manner similar to less accessible CNS structures.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02262-02 NPB

PERIOD COVERED

October 1, 1985 through September 30,1986

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

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PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Myles J. Jaffe, O.D., Senior Staff Fellow, Neuropsychiatry Branch, IRP, NIMH

Dr. Craig N. Karson, Staff Psychiatrist, Section on Clinical Neuropsychiatry, NPB, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	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.)*

The ganzfeld electroretinogram has revealed that both dopaminergic blockers and GABA potentiators have an inhibitory effect on human rods and cones. In a related clinical study, we have repeatedly shown the blue-sensitive cone system to be altered in male drug-free patients with schizophrenia when compared with age- and sex-matched controls. These results suggest that the neuromodulators of the retina may be altered by psychoactive drugs and psychiatric disease in a manner similar to less accessible CNS structures.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02263-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Haloperidol Pharmacodynamics and Clinical Response in Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Darrell G. Kirch, M.D., Senior Staff Fellow, Neuropsychiatry Branch, IRP, NIMH

Dr. Llewellyn B. Bigelow, Associate Clinical Director for the William A. White Division, Saint Elizabeths Hospital; Dr. Gregory M. Straw, Medical Staff Fellow, NPB, IRP, NIMH; Dr. George Jaskiw, Medical Staff Fellow, NPB, IRP, NIMH; Dr. Markku Linnoila, NIAAA; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH; Dr. Greg Gerhardt, University of Colorado Health Sciences Center; Dr. Robert Freedman, University of Colorado Health Sciences Center

COOPERATING UNITS *(if any)*

NIAAA; University of Colorado Health Sciences Center

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Psychopharmacology

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.5	.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 part of a standardized research sequence in the NIMH Intramural Clinical Program located at Saint Elizabeths, patients with schizophrenia are withdrawn from neuroleptic medication and then (after clinical relapse) treated with a fixed dose of haloperidol. This has in turn allowed initiation of a variety of studies regarding the pharmacokinetics of haloperidol. Other pharmacological issues examined in these patients are drug-drug interactions (specifically involving haloperidol and both nicotine and retinoic acid). In addition, basic science investigations regarding these drugs are being conducted.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02263-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Haloperidol Pharmacodynamics and Clinical Response in Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Darrell G. Kirch, M.D., Senior Staff Fellow, Neuropsychiatry Branch, IRP, NIMH

Dr. Llewellyn B. Bigelow, Associate Clinical Director for the William A. White Division, Saint Elizabeths Hospital; Dr. Gregory M. Straw, Medical Staff Fellow, NPB, IRP, NIMH; Dr. George Jaskiw, Medical Staff Fellow, NPB, IRP, NIMH; Dr. Markku Linnoila, NIAAA; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH; Dr. Greg Gerhardt, University of Colorado Health Sciences Center; Dr. Robert Freedman, University of Colorado Health Sciences Center

COOPERATING UNITS *(if any)*

NIAAA; University of Colorado Health Sciences Center

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Psychopharmacology

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.5	.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.)*

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02264-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Post Mortem Brain Tissue Examination in Psychiatric Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Joel E. Kleinman, M.D., Ph.D., Chief, Section on Clinical Brain Studies, NPB, IRP, NIMH

Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH; Dr. Craig N. Karson, Staff Psychiatrist, NPB, IRP, NIMH; Dr. Esa Korpi, State Alcohol Monopoly, Helsinki, Finland; Dr. Markku Linnoila, NIAAA, NIMH; Dr. Farouk Karoum, Chemist, NPB, IRP, NIMH; Dr. Daniel Weinberger, Chief, Section on Clinical Neuropsychiatry, NPB, IRP, NIMH; Dr. Anita Feenstra, Visting Associate, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

State Alcohol Monopoly, Helsinki, Finland; NIAAA; Johns Hopkins University; Clinical Neuroscience Branch, NIMH

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Clinical Brain Studies

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	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.)*

Postmortem studies in psychiatric disorders antemies to be a useful method for testing hypotheses. New findings include the following: (1) Decreased tritiated clonidine binding in the locus coeruleus of schizophrenic patients; (2) Increased methionine-enkephalin in the substantia nigra of schizophrenic patients; (3) Increased serotonin (5-HT) and 5-hydroxy-indoleacetic acid (5-HIAA) in basal ganglia and occipital cortex, respectively in schizophrenic patients; and (4) Decreases in 5-HT and 5-HIAA in hypothalamus and nucleus accumbens, respectively in suicides.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02264-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH; Dr. Craig N. Karson, Staff Psychiatrist, NPB, IRP, NIMH; Dr. Esa Korpi, State Alcohol Monopoly, Helsinki, Finland; Dr. Markku Linnoila, NIAAA, NIMH; Dr. Farouk Karoum, Chemist, NPB, IRP, NIMH; Dr. Daniel Weinberger, Chief, Section on Clinical Neuropsychiatry, NPB, IRP, NIMH; Dr. Anita Feenstra, Visting Associate, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

State Alcohol Monopoly, Helsinki, Finland; NIAAA; Johns Hopkins University; Clinical Neuroscience Branch, NIMH

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Clinical Brain Studies

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	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.)*

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02265-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Catecholamine Binding Site Changes in Human Post Mortem Tissue

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Grant N. Ko, M.D., Senior Staff Fellow, NPB, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Clinical Brain Studies Section

INSTITUTE AND LOCATION

NIMH, Saint Elizbeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	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.)*

Project was terminated when principal investigator moved to another laboratory outside NIMH.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02265-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

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Grant N. Ko, M.D., Senior Staff Fellow, NPB, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Clinical Brain Studies Section

INSTITUTE AND LOCATION

NIMH, Saint Elizbeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	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.)*

Project was terminated when principal investigator moved to another laboratory outside NIMH.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02266-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Quantitative Assessment of Motor Function in Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

James B. Lohr, M.D., Medical Staff Fellow, NPB, IRP, NIMH

Dr. Dilip V. Jeste, Medical Officer, NPB, IRP, NIMH; Dr. Jerome Sanes, National Institute of Neurological and Communicative Disorders and Stroke, NIH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

NINCDS, NIH

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	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 due to inactivity in the past year.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02266-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

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James B. Lohr, M.D., Medical Staff Fellow, NPB, IRP, NIMH

Dr. Dilip V. Jeste, Medical Officer, NPB, IRP, NIMH; Dr. Jerome Sanes, National Institute of Neurological and Communicative Disorders and Stroke, NIH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

NINCDS, NIH

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	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 due to inactivity in the past year.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02267-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Brain Electrical Activity Mapping in Neuropsychiatric Patients

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dr. Craig N. Karson, Staff Psychiatrist, NPB, IRP, NIMH

Dr. Terry Goldberg, Special Expert, NPB, IRP, NIMH; Dr. Karen F. Berman, Staff Psychiatrist, NPB, IRP, NIMH; Dr. Ralph Fawcett, Medical Staff Fellow, NPB, IRP, NIMH; Dr. Richard Coppola, Sr. Engineer Officer, NPB, IRP, NIMH, Dr. Daniel R. Weinberger, Chief, Section on Clinical Neuropsychiatry, NPB, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Clinical Neuropsychiatry

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1	.5	.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 promise that EEG might provide a non-invasive glimpse of brain activity in schizophrenia has recently been enhanced by computerized mapping techniques. These "maps" digest a vast amount of information and translate them into a highly interpretable form. Unfortunately artifact, such as eye movement can be included in such maps, leading to serious misinterpretations. We are currently examining computerized EEG activity mapping (CEAM) in medication-free chronic schizophrenic patients with a special attention the role of eye movement artifact. In addition, besides examining the patients in the resting state, we are stimulating the patients with medications such as apomorphine and cognitive tests specially designed to highlight the pathological processess in schizophrenia.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02267-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Brain Electrical Activity Mapping in Neuropsychiatric Patients

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dr. Craig N. Karson, Staff Psychiatrist, NPB, IRP, NIMH

Dr. Terry Goldberg, Special Expert, NPB, IRP, NIMH; Dr. Karen F. Berman, Staff Psychiatrist, NPB, IRP, NIMH; Dr. Ralph Fawcett, Medical Staff Fellow, NPB, IRP, NIMH; Dr. Richard Coppola, Sr. Engineer Officer, NPB, IRP, NIMH, Dr. Daniel R. Weinberger, Chief, Section on Clinical Neuropsychiatry, NPB, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Clinical Neuropsychiatry

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1	.5	.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.)*

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02268-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

The Clinical Phenomenology of Multiple Personality Disorder

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Frank W. Putnam, M.D., Staff Psychiatrist, Neuropsychiatry Branch, IRP, NIMH

Dr. E.A. Silberman, USUHS; Dr. Robert Post, Biological Psychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

USUHS
Biological Psychiatry Branch, IRP, NIMH

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.33	.33	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 syndrome of multiple personality disorder (MPD) is poorly characterized although the total number of identified cases has increased by over 2000% in the last five years compared to the 200 years prior. In an attempt to better delineate the clinical phenomenology of MPD, cases meeting DSM-III criteria are collected on a standardized questionnaire (The NIMH Clinician's Questionnaire on Multiple Personality). This study has documented the existence of a clinical syndrome characterized by a core of depressive and dissociative symptoms and a childhood history of significant trauma, primarily child abuse.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02268-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

The Clinical Phenomenology of Multiple Personality Disorder

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Frank W. Putnam, M.D., Staff Psychiatrist, Neuropsychiatry Branch, IRP, NIMH

Dr. E.A. Silberman, USUHS; Dr. Robert Post, Biological Psychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

USUHS
Biological Psychiatry Branch, IRP, NIMH

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.33	.33	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.)*

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02269-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

The Development, Reliability and Validity of a Dissociation Scale

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Frank W. Putnam, M.D., Staff Psychiatrist, Neuropsychiatry Branch, IRP, NIMH

Dr. Eve Bernstein, Department of Psychology, American University

COOPERATING UNITS *(if any)*

Department of Psychology, American University

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.33	.33	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 short, self-administered questionnaire has been developed and tested that reliably and validly measures frequency and types of dissociative phenomena. This instrument has been administered to a wide variety of psychiatric patient groups as well as normal control subjects and documents a continuum of symptoms of dissociation and depersonalization across these samples. This scale has been adopted by more than 20 research projects around the country and is currently being used by the National Academy of Sciences in a large scale study of posttraumatic stress disorder in Vietnam Veterans.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02269-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

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PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Frank W. Putnam, M.D., Staff Psychiatrist, Neuropsychiatry Branch, IRP, NIMH

Dr. Eve Bernstein, Department of Psychology, American University

COOPERATING UNITS *(if any)*

Department of Psychology, American University

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.33	.33	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 short, self-administered questionnaire has been developed and tested that reliably and validly measures frequency and types of dissociative phenomena. This instrument has been administered to a wide variety of psychiatric patient groups as well as normal control subjects and documents a continuum of symptoms of dissociation and depersonalization across these samples. This scale has been adopted by more than 20 research projects around the country and is currently being used by the National Academy of Sciences in a large scale study of posttraumatic stress disorder in Vietnam Veterans.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02270-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

The Psychophysiology of Multiple Personality

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Frank W. Putnam, M.D., Staff Psychiatrist, Neuropsychiatry Branch, IRP, NIMH

Dr. Karen F. Berman, Staff Psychiatrist, NPB, IRP, NIMH; Dr. Daniel Weinberger, Chief, Clinical Neuropsychiatry Section, NPB, IRP, NIMH; Dr. Richard Coppola, Engineer, Clinical Neuropsychiatry Section, NPB, IRP, NIMH; Dr. Robert M. Post, Biological Psychiatry Branch, IRP, NIMH; Dr. Theodore Zahn, Laboratory of Psychology and Psychopathology, BPB, NIMH;

COOPERATING UNITS *(if any)*

Biological Psychiatry Branch, IRP, NIMH

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.33	.33	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 seeks to investigate reported physiological differences that may exist across the alternate states of consciousness personified in the alter personalities of multiple personality disorder (MPD) patients. Measures incorporated in the study included: visual and auditory evoked potentials, EEG, cerebral blood flow, autonomic nervous system activity (galvanic skin response, heart rate, blood pressure, skin temperature, respiration) and immune system and endocrine system measures.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02270-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

The Psychophysiology of Multiple Personality

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Frank W. Putnam, M.D., Staff Psychiatrist, Neuropsychiatry Branch, IRP, NIMH

Dr. Karen F. Berman, Staff Psychiatrist, NPB, IRP, NIMH; Dr. Daniel Weinberger, Chief, Clinical Neuropsychiatry Section, NPB, IRP, NIMH; Dr. Richard Coppola, Engineer, Clinical Neuropsychiatry Section, NPB, IRP, NIMH; Dr. Robert M. Post, Biological Psychiatry Branch, IRP, NIMH; Dr. Theodore Zahn, Laboratory of Psychology and Psychopathology, BPB, NIMH;

COOPERATING UNITS *(if any)*

Biological Psychiatry Branch, IRP, NIMH

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.33	.33	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 seeks to investigate reported physiological differences that may exist across the alternate states of consciousness personified in the alter personalities of multiple personality disorder (MPD) patients. Measures incorporated in the study included: visual and auditory evoked potentials, EEG, cerebral blood flow, autonomic nervous system activity (galvanic skin response, heart rate, blood pressure, skin temperature, respiration) and immune system and endocrine system measures.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02271-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Fenfluramine and Chronic Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

David Shore, M.D., Staff Psychiatrist, Neuropsychiatry Branch, IRP, NIMH; Richard Jed Wyatt, M.D., Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Aging

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	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 completed and terminated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02271-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Fenfluramine and Chronic Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

David Shore, M.D., Staff Psychiatrist, Neuropsychiatry Branch, IRP, NIMH; Richard Jed Wyatt, M.D., Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Aging

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	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 completed and terminated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02272-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Sodium Fluoride Treatment of Alzheimer's Disease (AD)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

David Shore, M.D., Staff Psychiatrist, Neuropsychiatry Branch, IRP, NIMH; Richard Jed Wyatt, M.D., Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Aging

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	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 completed and terminated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02272-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Sodium Fluoride Treatment of Alzheimer's Disease (AD)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

David Shore, M.D., Staff Psychiatrist, Neuropsychiatry Branch, IRP, NIMH; Richard Jed Wyatt, M.D., Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Aging

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	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 completed and terminated.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02273-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

White House Cases: Predictors of Future Violence

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

David Shore, M.D., Staff Psychiatrist, NPB, IRP, NIMH

C. Richard Filson, Ed.D., Richardson Division, SEH; Kenneth Baker, Behavioral Research Section, U.S. Secret Service; Dr. Charles Kinderman, Bureau of Justice Statistics, U.S. Department of Justice; Ken Candell, Uniform Crime Reporting Division; William Garvie, Identification Division, FBI

COOPERATING UNITS *(if any)*

Richardson Division, Saint Elizabeths Hospital, Washington, D.C.; Behavioral Research Section, Intelligence Division, U.S. Secret Service; Bureau of Justice Statistics, U.S. Department of Justice; Uniform Crime Reporting Division and Identification Division, FBI

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Aging

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.25	.25	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 studies of White House Cases (WHCs) is being conducted. Data from the FBI regarding age and gender specific rates of arrest for various crimes in the general population are being analyzed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02273-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

White House Cases: Predictors of Future Violence

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

David Shore, M.D., Staff Psychiatrist, NPB, IRP, NIMH

C. Richard Filson, Ed.D., Richardson Division, SEH; Kenneth Baker, Behavioral Research Section, U.S. Secret Service; Dr. Charles Kinderman, Bureau of Justice Statistics, U.S. Department of Justice; Ken Candell, Uniform Crime Reporting Division; William Garvie, Identification Division, FBI

COOPERATING UNITS *(if any)*

Richardson Division, Saint Elizabeths Hospital, Washington, D.C.; Behavioral Research Section, Intelligence Division, U.S. Secret Service; Bureau of Justice Statistics, U.S. Department of Justice; Uniform Crime Reporting Division and Identification Division, FBI

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Aging

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.25	.25	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 studies of White House Cases (WHCs) is being conducted. Data from the FBI regarding age and gender specific rates of arrest for various crimes in the general population are being analyzed.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02274-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Exploration of New Methods for Treatment of Intractable Epilepsy

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Janice Stevens, M.D., Medical Officer, Neuropsychiatry Branch, IRP, NIMH

Dr. William J. Freed, Chief, Preclinical Neurosciences Section, NPB, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Aging

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1	.5	.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 an attempt to devise more effective methods for treatment of epilepsy that is intractable to conventional modern medical therapy or surgical intervention, we are exploring the feasibility of brain grafts of GABAergic brain tissue to affected brain areas in rat models of epilepsy. We have developed two satisfactory experimental epilepsy models in the laboratory: (1) audiogenic seizures in genetically predisposed rats and amygdala kindling. Grafts of fetal cerebellar tissue are being placed in critical sites where GABAergic agents have been shown to arrest seizures.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02274-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Exploration of New Methods for Treatment of Intractable Epilepsy

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Janice Stevens, M.D., Medical Officer, Neuropsychiatry Branch, IRP, NIMH

Dr. William J. Freed, Chief, Preclinical Neurosciences Section, NPB, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Aging

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1	.5	.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 an attempt to devise more effective methods for treatment of epilepsy that is intractable to conventional modern medical therapy or surgical intervention, we are exploring the feasibility of brain grafts of GABAergic brain tissue to affected brain areas in rat models of epilepsy. We have developed two satisfactory experimental epilepsy models in the laboratory: (1) audiogenic seizures in genetically predisposed rats and amygdala kindling. Grafts of fetal cerebellar tissue are being placed in critical sites where GABAergic agents have been shown to arrest seizures.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02275-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Search for Virus in CSF and Postmortem Brain of Patients with Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Janice R. Stevens, M.D., Medical Officer, Neuropsychiatry Branch, IRP, NIMH

Dr. Richard Ziegler, Department of Microbiology, University of Minnesota; Dr. Yen-Nung Wang, Visiting Associate, Neuropsychiatry Branch, IRP, NIMH; Dr. Ashley Haase, Department of Microbiology, University of Minnesota; Dr. Joel E. Kleinman, Chief, Section on Clinical Brain Studies, NPB, IRP, NIMH; Dr. David Asher, NINCDS, Bethesda, Maryland; Dr. Joan Schwartz, Chemist, Laboratory of Preclinical Pharmacology, IRP, NIMH

COOPERATING UNITS *(if any)*

Department of Microbiology, University of Minnesota
Food and Drug, NINCDS
Laboratory of Preclinical Pharmacology, IRP, NIMH

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Aging

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1	.5	.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.)*

Based on substantial evidence that an infectious agent or agents may play a role in the etiology of at least a subtype of schizophrenic illness, we are searching for evidence of an infectious or toxic substance in schizophrenic brains. Studies undertaken to date include immunocytochemical investigations for antigens to cytomegalovirus (CMV), herpes simplex virus (HSV), varicella virus, rubella and mumps. Although sporadic cases have shown positive results with immunocytochemical studies, these have been inconsistent and rare. We have also undertaken in situ hybridization probes for CMV, and cultivation of schizophrenic and control brain specimens on cultures of human and non-human neural tissue. Using special stains for glia we have evaluated the brains of guinea pigs and primates previously innoculated with schizophrenic and control brain tissue. During the past year we have investigated the effects of cerebrospinal fluid and sterile brain tissue from schizophrenic patients on the growth, peptide production and morphology of cultured human neuroblastoma cells. Changes in growth rate have thus far been noted following treatment of cells with fresh CSF from two schizophrenic cases. The remaining samples studied to date (six schizophrenic, seven normals) have shown no changes in any of the three parameters under study and no other differences between normals and schizophrenics have emerged.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02275-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Search for Virus in CSF and Postmortem Brain of Patients with Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Janice R. Stevens, M.D., Medical Officer, Neuropsychiatry Branch, IRP, NIMH

Dr. Richard Ziegler, Department of Microbiology, University of Minnesota; Dr. Yen-Nung Wang, Visiting Associate, Neuropsychiatry Branch, IRP, NIMH; Dr. Ashley Haase, Department of Microbiology, University of Minnesota; Dr. Joel E. Kleinman, Chief, Section on Clinical Brain Studies, NPB, IRP, NIMH; Dr. David Asher, NINCDS, Bethesda, Maryland; Dr. Joan Schwartz, Chemist, Laboratory of Preclinical Pharmacology, IRP, NIMH

COOPERATING UNITS *(if any)*

Department of Microbiology, University of Minnesota
Food and Drug, NINCDS
Laboratory of Preclinical Pharmacology, IRP, NIMH

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Aging

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1	.5	.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.)*

Based on substantial evidence that an infectious agent or agents may play a role in the etiology of at least a subtype of schizophrenic illness, we are searching for evidence of an infectious or toxic substance in schizophrenic brains. Studies undertaken to date include immunocytochemical investigations for antigens to cytomegalovirus (CMV), herpes simplex virus (HSV), varicella virus, rubella and mumps. Although sporadic cases have shown positive results with immunocytochemical studies, these have been inconsistent and rare. We have also undertaken in situ hybridization probes for CMV, and cultivation of schizophrenic and control brain specimens on cultures of human and non-human neural tissue. Using special stains for glia we have evaluated the brains of guinea pigs and primates previously innoculated with schizophrenic and control brain tissue. During the past year we have investigated the effects of cerebrospinal fluid and sterile brain tissue from schizophrenic patients on the growth, peptide production and morphology of cultured human neuroblastoma cells. Changes in growth rate have thus far been noted following treatment of cells with fresh CSF from two schizophrenic cases. The remaining samples studied to date (six schizophrenic, seven normals) have shown no changes in any of the three parameters under study and no other differences between normals and schizophrenics have emerged.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02276-01 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

TITLE OF PROJECT *(60 characters or less. Title must fit on one line between the borders.)*

Localization of Met^5-Enkephalin-Arg^6-Phe^7-Like Immunoreactivity

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Yen-Nung Wang, M.D., Visiting Associate, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Aging

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	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 is continued under number Z01 MH 02319-01 NPB.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02276-01 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Localization of Met^5-Enkephalin-Arg^6-Phe^7-Like Immunoreactivity

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Yen-Nung Wang, M.D., Visiting Associate, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Aging

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	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 is continued under number Z01 MH 02319-01 NPB.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02277-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Regional Cerebral Blood Flow in Neuropsychiatric Patients and in Normal Subjects

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Daniel Weinberger, M.D., Chief, Section on Clinical Neuropsychiatry, NPB, NIMH; Karen Faith Berman, M.D., Staff Psychiatrist, NPB, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Clinical Neuropsychiatry

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
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.)*

Using the Xenon133 inhalation technique, the regional cerebral blood flow (rCBF) lab within the Section on Clinical Neuropsychiatry carries out investigations of rCBF (as an indicator of regional cortical metabolism) in a variety of neuropsychiatric patients and in normal subjects. Patient populations, including those with chronic schizophrenia, affective disorder, obsessive-compusive disorder, Huntington's disease, Parkinson's disease, Alzheimer's disease, and dyslexia are studied before and during various exploratory and therapeutic interventions. Normal control subjects matched for each patient study are investigated concurrently. Cortical metabolic concomitants of states of normal cognition and consciousness are also being explored. The Xenon133 method allows for multiple determinations of rCBF in a single individual who can thus serve as his or her own control while being studied serially under various cognitive and/or medication conditions. This allows paradigms to be designed to specifically test hypotheses about regional cortical function in disease states and normal higher cognitive function and to specifically monitor experimental and therapeutic inteventions in neuropsychiatric disorders. Careful and creative application of this versatile tool has produced important results. Experiments tailored to explore dorsolateral prefrontal cortex (DLPFC), an area of special interest in schizophrenia, have shown this area to be de-activated in patients with schizophrenia under conditions of cognitively specific, regionally selective demand of this area - conditions under which normals increase metabolism to DLPFC. In contrast Huntington's disease patients who are as cognitively impaired as schizophrenics, do not show DLPFC rCBF abnormality, but rather rCBF patterns similar to normal subjects. This is important evidence for the existence of subcortical dementia, which, until now, has been questioned by some.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02277-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Regional Cerebral Blood Flow in Neuropsychiatric Patients and in Normal Subjects

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Daniel Weinberger, M.D., Chief, Section on Clinical Neuropsychiatry, NPB, NIMH; Karen Faith Berman, M.D., Staff Psychiatrist, NPB, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Clinical Neuropsychiatry

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
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.)*

Using the Xenon133 inhalation technique, the regional cerebral blood flow (rCBF) lab within the Section on Clinical Neuropsychiatry carries out investigations of rCBF (as an indicator of regional cortical metabolism) in a variety of neuropsychiatric patients and in normal subjects. Patient populations, including those with chronic schizophrenia, affective disorder, obsessive-compuslive disorder, Huntington's disease, Parkinson's disease, Alzheimer's disease, and dyslexia are studied before and during various exploratory and therapeutic interventions. Normal control subjects matched for each patient study are investigated concurrently. Cortical metabolic concomitants of states of normal cognition and consciousness are also being explored. The Xenon133 method allows for multiple determinations of rCBF in a single individual who can thus serve as his or her own control while being studied serially under various cognitive and/or medication conditions. This allows paradigms to be designed to specifically test hypotheses about regional cortical function in disease states and normal higher cognitive function and to specifically monitor experimental and therapeutic inteventions in neuropsychiatric disorders. Careful and creative application of this versatile tool has produced important results. Experiments tailored to explore dorsolateral prefrontal cortex (DLPFC), an area of special interest in schizophrenia, have shown this area to be de-activated in patients with schizophrenia under conditions of cognitively specific, regionally selective demand of this area - conditions under which normals increase metabolism to DLPFC. In contrast Huntington's disease patients who are as cognitively impaired as schizophrenics, do not show DLPFC rCBF abnormality, but rather rCBF patterns similar to normal subjects. This is important evidence for the existence of subcortical dementia, which, until now, has been questioned by some.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02278-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Structural Brain Imaging in Schizophrenic Patients and Normal Subjects

PRINCIPAL INVESTIGATOR *(List other professionel personnel below the Principal Investigator.) (Name, title, laboratory, end institute affiliation)*

Daniel R. Weinberger, M.D., Chief, Section on Clinical Neuropsychiatry, NPB, IRP, NIMH

Dr. George Jaskiw, Visiting Associate, Section on Clinial Neuropsychiatry, NPB, IRP, NIM; Dr. Barbara Illowsky, Medical Staff Fellow, Section on Clinical Brain Studies, NPB, IRP, NIMH; Dilip V. Jeste, Medical Officer, NPB, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH; Dr. Allen Doran, Clinical Research Associate, Clinical Neuroscience Branch, NIMH; Dr. Carl Feinstein, Assistant Professor of Psychiatry, George Washington University; Dr. David Pickar, Chief, Section on Clinical Studies, Clinical Neuroscience Branch, NIMH

COOPERATING UNITS *(il any)*

Clinical Neuroscience Branch, NIMH
George Washington University

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Clinical Neuropsychiatry

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	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.)*

The project on structural brain imaging investigates structural pathology of the brains of schizophrenic patients housed in the William A. White research units using x-ray computerized tomography (CT). Patients are compared to matched normal controls. The most recent study, a culmination of four years of data collection, compared 73 schizophrenic patients to 30 normal volunteer controls. This project is a replication and extension of the previous work done in this area in the branch. Using standardized techniques four brain areas were examined: lateral ventricles, third ventricles, cortical (parieto-occipital) areas, and prefrontal cortex. In this sample, the lateral and third ventricles continued to be significantly larger in patients than controls. A potentially exciting new finding was that though there were essentially no differences between patients and controls in cortical atrophy in the parieto-occipital distribution, the schizophrenic patients showed substantially greater atrophy in the prefrontal distribution, localizing the cortical changes to this area. Further, in a subgroup of 18 drug-free and 22 medicated patients, the CT abnormalities were correlated with regional cerebral blood flow (rCBF) using the radioactive ^{133}Xenon inhalation technique. Relationships were found between the neurophysiological measurements of CT scanning, especially in the prefrontal cortex and ventricular areas. This work is being amplified to search for clinical and biological correlations of ventricular enalargement and prefrontal atrophy, particularly with respect to other signs of prefrontal pathology, e.g., rCBF, EEG, PET data. In addition, we are in the process of following up earlier patients and rescanning them after 7-9 years.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02278-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

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PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Daniel R. Weinberger, M.D., Chief, Section on Clinical Neuropsychiatry, NPB, IRP, NIMH

Dr. George Jaskiw, Visiting Associate, Section on Clinial Neuropsychiatry, NPB, IRP, NIM; Dr. Barbara Illowsky, Medical Staff Fellow, Section on Clinical Brain Studies, NPB, IRP, NIMH; Dilip V. Jeste, Medical Officer, NPB, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH; Dr. Allen Doran, Clinical Research Associate, Clinical Neuroscience Branch, NIMH; Dr. Carl Feinstein, Assistant Professor of Psychiatry, George Washington University; Dr. David Pickar, Chief, Section on Clinical Studies, Clinical Neuroscience Branch, NIMH

COOPERATING UNITS *(if any)*

Clinical Neuroscience Branch, NIMH
George Washington University

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Clinical Neuropsychiatry

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	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.)*

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02279-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Comparison of Neuroleptic Induced Supersensitivity in Mice

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Alex Wisniewski, M.D., Medical Staff Fellow, NPB, IRP, NIMH

Dr. Dilip V. Jeste, Medical Officer, NPB, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Aging

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	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 because the principal investigator left the NIMH.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02279-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

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PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Alex Wisniewski, M.D., Medical Staff Fellow, NPB, IRP, NIMH

Dr. Dilip V. Jeste, Medical Officer, NPB, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Aging

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	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 because the principal investigator left the NIMH.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02280-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Brain Tissue Transplantation in Primates

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Richard Jed Wyatt, M.D., Chief, Neuropsychiatry Branch, IRP, NIMH

Dr. William J. Freed, Chief, Preclinical Neurosciences Section, NPB, IRP, NIMH; Dr. Richard Nakamura, LPP, IRP, NIMH; Dr. Donald Price, Johns Hopkins Hospital; Dr. Cheryl Kitt, Johns Hopkins Hospital

COOPERATING UNITS *(if any)*

LPP, NIMH
Johns Hopkins Hospital

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	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.)*

To advance the work already performed in our laboratory with rats, fetal substantia nigra or adrenal medulla was grafted to the denervated caudate of the the rhesus monkey in our continuing research on brain tissue transplantation. Success for graft survival has been good in the last year.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02280-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

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PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Richard Jed Wyatt, M.D., Chief, Neuropsychiatry Branch, IRP, NIMH

Dr. William J. Freed, Chief, Preclinical Neurosciences Section, NPB, IRP, NIMH; Dr. Richard Nakamura, LPP, IRP, NIMH; Dr. Donald Price, Johns Hopkins Hospital; Dr. Cheryl Kitt, Johns Hopkins Hospital

COOPERATING UNITS *(if any)*

LPP, NIMH
Johns Hopkins Hospital

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	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.)*

To advance the work already performed in our laboratory with rats, fetal substantia nigra or adrenal medulla was grafted to the denervated caudate of the the rhesus monkey in our continuing research on brain tissue transplantation. Success for graft survival has been good in the last year.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02281-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Neural Tissue Microchip Interface

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

A. Paul Oliver, Physiologist, Neuropsychiatry Branch, IRP, NIMH

Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH; Dr. Myles Jaffe, Senior Staff Fellow, NPB, IRP, NIMH; Dr. Marty C. Peckerar, Naval Research Laboratory, Microelectronics Processing Facility, Washington, D.C.

COOPERATING UNITS *(if any)*

Naval Research Laboratory, Microelectronics Processing Facility, Washington, D.C.

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1	1	0

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.)*

The eventual development of a neural prosthesis requires studies related to identifing suitable materials, reliability, computer interfacing, software development, overall system development. This objective can be partially met by designing and testing a simplified system. Our first approach to this was a simple chip device capable of monitoring 30 cultured nerve cells. The device is an integral part of a computer system. To date we have identified some problems with materials, and some with mechanical design. We are also attempting to co-culture retina and retinal targeted tissue such as superior colliculus to test the potential for two-way communication.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02281-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

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PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

A. Paul Oliver, Physiologist, Neuropsychiatry Branch, IRP, NIMH

Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH; Dr. Myles Jaffe, Senior Staff Fellow, NPB, IRP, NIMH; Dr. Marty C. Peckerar, Naval Research Laboratory, Microelectronics Processing Facility, Washington, D.C.

COOPERATING UNITS *(if any)*

Naval Research Laboratory, Microelectronics Processing Facility, Washington, D.C.

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	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.)*

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02282-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Neurovirology and Neuroimmunology of Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnal below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Darrell G. Kirch, M.D., Senior Staff Fellow, Neuropsychiatry Branch, IRP, NIMH

Dr. Anita Feenstra, Visiting Associate, NPB, IRP, NIMH; Dr. John G. Knight, Research Fellow, Clinical Neuroscience Branch, NIMH; Dr. Nicholas M. Papadopoulos, Clinical Chemistry Service, NIH; Dr. Daniel R. Weinberger, Chief, Section on Clinical Neuropsychiatry, NPB, IRP, NIMH; Dr. Joel E. Kleinman, Chief, Section on Clinical Brain Studies, NPB, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

Clinical Neuroscience Branch, NIMH
Clinical Chemistry Service, NIH

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Psychopharmacology

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.5	.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 project on neurovirology and neuroimmunology has continued its efforts to provide evidence that the pathogenesis of schizophrenia involves either an infectious process by a viral agent and/or an autoimmune reaction involving central nervous system tissue autoantibodies.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02282-02 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

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Darrell G. Kirch, M.D., Senior Staff Fellow, Neuropsychiatry Branch, IRP, NIMH

Dr. Anita Feenstra, Visiting Associate, NPB, IRP, NIMH; Dr. John G. Knight, Research Fellow, Clinical Neuroscience Branch, NIMH; Dr. Nicholas M. Papadopoulos, Clinical Chemistry Service, NIH; Dr. Daniel R. Weinberger, Chief, Section on Clinical Neuropsychiatry, NPB, IRP, NIMH; Dr. Joel E. Kleinman, Chief, Section on Clinical Brain Studies, NPB, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

Clinical Neuroscience Branch, NIMH
Clinical Chemistry Service, NIH

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Psychopharmacology

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.5	.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.)*

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02309-01 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

The Brief Psychiatric Rating Scale as a Ward Daily Rating System

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Llewellyn B. Bigelow, M.D., Associate Clinical Director for Research at Saint Elizabeths Hospital, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	.5	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 Brief Psychiatric Rating Scale is one of the most popular general rating scales used in clinical psychiatric research. It is generally used as a single point interview based instrument. We have modified the instructions and put in scaling points to enhance the reliability of this instrument. Furthermore, a training program has been devised so that interrater reliability can be achieved in a clinical setting using nursing staff as raters. Programs and methods for processing ratings twice daily have been developed which enable investigators to have rapid online access to meaningful information. This can be of great assistance in making decisions regarding protocol format and individual patient treatment.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02309-01 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

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PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Llewellyn B. Bigelow, M.D., Associate Clinical Director for Research at Saint Elizabeths Hospital, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	.5	1

CHECK APPROPRIATE BOX(ES)

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☐ (a1) Minors

☐ (a2) Interviews

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

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02310-01 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Treatment of Migraine with Anionic Polyelectrolytes

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Llewellyn B. Bigelow, M.D., Associate Clinical Director for the William A. White Division, Saint Elizabeths Hospital

Dr. Ernst Thonnard, General Medical Officer, Saint Elizabeths Hospital

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.5	.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.)*

In previous studies on patients with migraine headaches we found that half had a low blood concentration of lymphocytes and of the herparin carrying basophil. Treatment with inhalations of heparin restored these blood indices to normal and was accompanied by a reduction in the severity and frequency of migraine headache. We report here data on the treatment of 34 migraine patients with heparin inhlalations and with the semisynthetic heparinoid, Pentosan Polysulfate (PNP). The migraine index of the 24 responding patients had a mean improvement of 79%. Cytochemical investigation of the white blood cells of responding patients prior to treatment indicated fewer than normal basophilic leukocytes ($p < 0.001$), in particular fewer large lymphocytes positive for nonspecific esterases (T-cells) ($p < 0.001$). These patients also had a lower percentage of lymphocytes positive for acid phosphatase ($p < 0.001$) and a greater percentage of lymphocytes positive for RNA ($p < 0.001$) compared to controls. Ten patients whose migraine headaches were closely related to their menstrual cycles were unresponsive to heparin or PNP. These patients had reduced levels of T-cells, but also total white cell and granulocyte counts were low, whereas basophil levels were in the normal range. In the responding patients, treatment with heparin or PNP either corrected these abnormalities or effected a shift towards normal, whereas in the clinically unresponsive patients, neither polyelectrolyte produced a change. These studies suggest that in the clinically responsive patients the pathophysiology of migraine is reflected in an immune system dysfunction and that the abnormalities in this system can be corrected by the administration of heparin-like substances. The lack of effect of heparin or PNP on the clinical course or hematologic abnormalities of those patients whose headaches were related to their menstrual cycle suggests a different pathophysiology for this subpopulation. The clinical results are sufficiently encouraging to warrant larger scale blind trials to determine the place of anionic polyelectrolytes in the treatment of migraine.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02310-01 NPB

PERIOD COVERED
October 1, 1985 through September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Treatment of Migraine with Anionic Polyelectrolytes

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
Llewellyn B. Bigelow, M.D., Associate Clinical Director for the William A. White Division, Saint Elizabeths Hospital

Dr. Ernst Thonnard, General Medical Officer, Saint Elizabeths Hospital

COOPERATING UNITS *(if any)*

LAB/BRANCH
Neuropsychiatry Branch

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.5	.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.)*

In previous studies on patients with migraine headaches we found that half had a low blood concentration of lymphocytes and of the herparin carrying basophil. Treatment with inhalations of heparin restored these blood indices to normal and was accompanied by a reduction in the severity and frequency of migraine headache. We report here data on the treatment of 34 migraine patients with heparin inhlalations and with the semisynthetic heparinoid, Pentosan Polysulfate (PNP). The migraine index of the 24 responding patients had a mean improvement of 79%. Cytochemical investigation of the white blood cells of responding patients prior to treatment indicated fewer than normal basophilic leukocytes ($p < 0.001$), in particular fewer large lymphocytes positive for nonspecific esterases (T-cells) ($p < 0.001$). These patients also had a lower percentage of lymphocytes positive for acid phosphatase ($p < 0.001$) and a greater percentage of lymphocytes positive for RNA ($p < 0.001$) compared to controls. Ten patients whose migraine headaches were closely related to their menstrual cycles were unresponsive to heparin or PNP. These patients had reduced levels of T-cells, but also total white cell and granulocyte counts were low, whereas basophil levels were in the normal range. In the responding patients, treatment with heparin or PNP either corrected these abnormalities or effected a shift towards normal, whereas in the clinically unresponsive patients, neither polyelectrolyte produced a change. These studies suggest that in the clinically responsive patients the pathophysiology of migraine is reflected in an immune system dysfunction and that the abnormalities in this system can be corrected by the administration of heparin-like substances. The lack of effect of heparin or PNP on the clinical course or hematologic abnormalities of those patients whose headaches were related to their menstrual cycle suggests a different pathophysiology for this subpopulation. The clinical results are sufficiently encouraging to warrant larger scale blind trials to determine the place of anionic polyelectrolytes in the treatment of migraine.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02311-01 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Ontogeny of Preprocholecystokinin, Proenkephalin and Tyrosine Hydroxylase in Rats

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Anne-Marie Duchemin, M.D., Visiting Fellow, Neuropsychiatry Branch, IRP, NIMH

Dr. Thanh Than Quach, Guest Researcher, Neuropsychiatry Branch, IRP, NIMH; Dr. Michael Iadarola, Guest Researcher, Neuropsychiatry Branch, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.33	.33	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 expression of the genes coding for cholecystokinin (CCK), enkephalin and tyrosine hydroxylase (TH) was studied pre- and post-natally in the rat brain by using the corresponding specific cDNA probes to quantify mRNA. In addition, specific radioimmunoassays were used to measure CCK-immunoreactive peptides (CCK-IR) and enkephalin immunoreactive peptides. For the study on developmental expression of the tyrosine hydroxylase gene, mRNA levels were measured comparatively in the substantia nigra and the locus coeruleus and the levels of noradrenaline, dopamine and their metabolites were measured at the same time.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02311-01 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.33	.33	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 expression of the genes coding for cholecystokinin (CCK), enkephalin and tyrosine hydroxylase (TH) was studied pre- and post-natally in the rat brain by using the corresponding specific cDNA probes to quantify mRNA. In addition, specific radioimmunoassays were used to measure CCK-immunoreactive peptides (CCK-IR) and enkephalin immunoreactive peptides. For the study on developmental expression of the tyrosine hydroxylase gene, mRNA levels were measured comparatively in the substantia nigra and the locus coeruleus and the levels of noradrenaline, dopamine and their metabolites were measured at the same time.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02312-01 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Neurotrophic Activity in Cerebrospinal Fluid of Schizophrenic Patients

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Anne-Marie Duchemin, M.D., Visiting Fellow, Neuropsychiatry Branch, IRP, NIMH

Dr. Thanh Than Quach, Guest Researcher, Neuropsychiatry Branch, IRP, NIMH; Dr. Charles Kaufmann, Staff Psychiatrist, Neuropsychiatry Branch, IRP, NIMH; Dr. Daniel Weinberger, Chief, Section on Clinical Neuropsychiatry, NPB, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.33	.33	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.)*

We tested the ability of CSF from neurologic and psychiatric patients to allow the survival in culture of sympathetic neurons from chicken embryo ganglia. The presence of a neurotrophic activity in the CSF of some schizophrenic patients will be discussed in correlation with neuroleptic treatment or cerebral ventricle enlargement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02312-01 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

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Anne-Marie Duchemin, M.D., Visiting Fellow, Neuropsychiatry Branch, IRP, NIMH

Dr. Thanh Than Quach, Guest Researcher, Neuropsychiatry Branch, IRP, NIMH; Dr. Charles Kaufmann, Staff Psychiatrist, Neuropsychiatry Branch, IRP, NIMH; Dr. Daniel Weinberger, Chief, Section on Clinical Neuropsychiatry, NPB, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.33	.33	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.)*

We tested the ability of CSF from neurologic and psychiatric patients to allow the survival in culture of sympathetic neurons from chicken embryo ganglia. The presence of a neurotrophic activity in the CSF of some schizophrenic patients will be discussed in correlation with neuroleptic treatment or cerebral ventricle enlargement.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02313-01 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Retroviral Activity in Lymphocytes of Patients with Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Anita Feenstra, Ph.D., Visiting Associate, Neuropsychiatry Branch, IRP, NIMH

Dr. Darrell G. Kirch, Senior Staff Fellow, Neuropsychiatry Branch, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.5	.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.)*

Cell cultures of lymphocytes of patients with schizophrenia are established. These cultures will be tested for the retrovirus-specific enzyme reverse transcriptase in order to investigate the hypothesis associating retroviral infection with the development of schizophrenia.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02313-01 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Retroviral Activity in Lymphocytes of Patients with Schizophrenia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Anita Feenstra, Ph.D., Visiting Associate, Neuropsychiatry Branch, IRP, NIMH

Dr. Darrell G. Kirch, Senior Staff Fellow, Neuropsychiatry Branch, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.5	.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.)*

Cell cultures of lymphocytes of patients with schizophrenia are established. These cultures will be tested for the retrovirus-specific enzyme reverse transcriptase in order to investigate the hypothesis associating retroviral infection with the development of schizophrenia.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02314-01 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Development of an Auditory Sort Test

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dr. Terry Goldberg, Special Expert, Neuropsychiatry Branch, IRP, NIMH

Dr. Daniel Weinberger, Chief, Section on Clinical Neuropsychiatry, NPB, IRP, NIMH; Dr. Craig Karson, Staff Psychiatrist, NPB, IRP, NIMH; Dr. Karen Berman, Staff Psychiatrist, NPB, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Clinical Neuropsychiatry

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.33	.33	0

CHECK APPROPRIATE BOX(ES)

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

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

Concept formation tasks with a set shifting component have proven sensitive to frontal lobe dysfunction. The Wisconsin Card Sort, perhaps the most widely known test of this class, activates prefrontal regions in most normal but no schizophrenic subjects. It is presented in the visual modality. To further validate the use of such a test and to facilitate cognitive activation in EEG - BEAM studies while reducing eye movement, an auditory analog of the card sort was developed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02314-01 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

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Dr. Daniel Weinberger, Chief, Section on Clinical Neuropsychiatry, NPB, IRP, NIMH; Dr. Craig Karson, Staff Psychiatrist, NPB, IRP, NIMH; Dr. Karen Berman, Staff Psychiatrist, NPB, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Clinical Neuropsychiatry

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.33	.33	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.)*

Concept formation tasks with a set shifting component have proven sensitive to frontal lobe dysfunction. The Wisconsin Card Sort, perhaps the most widely known test of this class, activates prefrontal regions in most normal but no schizophrenic subjects. It is presented in the visual modality. To further validate the use of such a test and to facilitate cognitive activation in EEG - BEAM studies while reducing eye movement, an auditory analog of the card sort was developed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02315-01 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Hierorchy and Sensitivity in Putative Frontal Lobe Tasks

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dr. Terry Goldberg, Special Expert, Neuropsychiatry Branch, IRP, NIMH

Dr. Daniel Weinberger, Chief, Section on Clinical Neuropsychiatry, NPB, IRP, NIMH; Dr. John Kelsoe, Section on Clinical Studies, Clinical Neuroscience Branch, NIMH

COOPERATING UNITS *(if any)*

Section on Clinical Studies, Clinical Neuroscience Branch, NIMH

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Clinical Neuropsychiatry

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.33	.33	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.)*

Various standardized neuropsychological tests are thought to tap frontal lobe function to varying degrees. These involve verbal fluency, multiple tracking, category formation, and hypothetico-deductive reasoning and set shifting. The differential performance of schizophrenic patients with physiological frontal lobe dysfunctions of these tasks is unknown. We are investigating the sensitivity of the tests and the possibility that there is a hierarchical arrangement of them.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02315-01 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Hierarchy and Sensitivity in Putative Frontal Lobe Tasks

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dr. Terry Goldberg, Special Expert, Neuropsychiatry Branch, IRP, NIMH

Dr. Daniel Weinberger, Chief, Section on Clinical Neuropsychiatry, NPB, IRP, NIMH; Dr. John Kelsoe, Section on Clinical Studies, Clinical Neuroscience Branch, NIMH

COOPERATING UNITS *(if any)*

Section on Clinical Studies, Clinical Neuroscience Branch, NIMH

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Clinical Neuropsychiatry

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.33	.33	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.)*

Various standardized neuropsychological tests are thought to tap frontal lobe function to varying degrees. These involve verbal fluency, multiple tracking, category formation, and hypothetico-deductive reasoning and set shifting. The differential performance of schizophrenic patients with physiological frontal lobe dysfunctions of these tasks is unknown. We are investigating the sensitivity of the tests and the possibility that there is a hierarchical arrangement of them.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02316-01 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

"Teaching" the Wisconsin Card Sort to Schizophrenic Patients

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Dr. Terry Goldberg, Special Expert, Neuropsychiatry Branch, IRP, NIMH

Dr. Daniel Weinberger, Chief, Section on Clinical Neuropsychiatry, NPB, IRP, NIMH; Dr. Karen Berman, Staff Psychiatrist, NPB, IRP, NIMH; Dr. Marvin Podd, O'Malley Division, Saint Elizabeths Hospital

COOPERATING UNITS *(if any)*

O'Malley Division, Saint Elizabeths Hospital

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Clinical Neuropsychiatry

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.33	.33	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 is known that schizophrenic patients perform poorly on the Wisconsin Card Sort Test. However, the precise cognitive mechanism that contributes to poor performance is unknown. The test itself involves the ability to categorize, respond to feedback, shift mental sets, use deductive reasoning, and maintain set in short term memory. The subject is requested to match cards of various types with target items on the basis of different parameters (shape, color or number). In this study, patients will be taught various aspects of the test in order to observe which interventions, if any, produce improvement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02316-01 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

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Dr. Terry Goldberg, Special Expert, Neuropsychiatry Branch, IRP, NIMH

Dr. Daniel Weinberger, Chief, Section on Clinical Neuropsychiatry, NPB, IRP, NIMH; Dr. Karen Berman, Staff Psychiatrist, NPB, IRP, NIMH; Dr. Marvin Podd, O'Malley Division, Saint Elizabeths Hospital

COOPERATING UNITS *(if any)*

O'Malley Division, Saint Elizabeths Hospital

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Clinical Neuropsychiatry

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.33	.33	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 is known that schizophrenic patients perform poorly on the Wisconsin Card Sort Test. However, the precise cognitive mechanism that contributes to poor performance is unknown. The test itself involves the ability to categorize, respond to feedback, shift mental sets, use deductive reasoning, and maintain set in short term memory. The subject is requested to match cards of various types with target items on the basis of different parameters (shape, color or number). In this study, patients will be taught various aspects of the test in order to observe which interventions, if any, produce improvement.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02317-01 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Peripheral and Central Metabolism of Ingested L-DOPA in Rats

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Farouk Karoum, Ph.D., Chemist, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Psychopharmacology

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	.5	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.)*

An attempt was made to assess the effects of increased body concentration of DA on the activities of catecholamine neurons in the periphery and brain. This was achieved by following the metabolism of ingested deuterated L-DOPA. It is assumed that after the ingestion of deuterated DOPA the excretion of deuterated dopamine and its metabolite will closely mimic the fate of ingested L-DOPA while changes in non-deuterated dopamine, norepinephrine and their metabolites will reflect upon the effects of increased body DA from ingested L-DOPA on peripheral and central catecholamine neurons.

Since L-DOPA is commonly coadministered with peripheral dopadecarboxylase inhibitors, the influence of two types of dopadecarboxylase inhibitors on the metabolism of L-DOPA were also evaluated. The inhibitors are carbidopa (a peripheral drug) and alphamethyldopa (a compound that easily crosses the blood brain barrier). These two inhibitors were selected because alphamethyldopa is a metabolite of carbidopa. The possibility exists that coadministration of carbidopa with L-DOPA may produce central effects that can be attributed to alphamethyldopa.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02317-01 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

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Farouk Karoum, Ph.D., Chemist, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Psychopharmacology

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	.5	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.)*

An attempt was made to assess the effects of increased body concentration of DA on the activities of catecholamine neurons in the periphery and brain. This was achieved by following the metabolism of ingested deuterated L-DOPA. It is assumed that after the ingestion of deuterated DOPA the excretion of deuterated dopamine and its metabolite will closely mimic the fate of ingested L-DOPA while changes in non-deuterated dopamine, norepinephrine and their metabolites will reflect upon the effects of increased body DA from ingested L-DOPA on peripheral and central catecholamine neurons.

Since L-DOPA is commonly coadministered with peripheral dopadecarboxylase inhibitors, the influence of two types of dopadecarboxylase inhibitors on the metabolism of L-DOPA were also evaluated. The inhibitors are carbidopa (a peripheral drug) and alphamethyldopa (a compound that easily crosses the blood brain barrier). These two inhibitors were selected because alphamethyldopa is a metabolite of carbidopa. The possibility exists that coadministration of carbidopa with L-DOPA may produce central effects that can be attributed to alphamethyldopa.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02318-01 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Effects of Retinoic Acids on Brain, Behavior, and Drug Interactions

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Gregory M. Straw, M.D., Clinical Research Associate, Preclinical Neurosciences Section, NPB, IRP, NIMH

Dr. Darrell Kirch, Associate Clinical Associate, NPB, IRP, NIMH; Dr. William J. Freed, Chief, Preclinical Neurosciences Section, NPB, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Preclinical Neurosciences Section

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.75	.75	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 on the effects of retinoic acids on brain, behavior and drug interactions investigates the pathophysiology of retinoic acid action in vivo. Rats are the current model but expansion into mouse and guinea pig models is anticipated. The primary focus of the rat model is the assay of the pharmacokinetics of the interaction of 13-cis-retinoic acid with neuroleptics. Early results have shown statistically significant changes in the blood levels of haloperidol and one of its metabolites after the concurrent administration of 13-cis-retinoic acid to rats.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02318-01 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Effects of Retinoic Acids on Brain, Behavior, and Drug Interactions

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Gregory M. Straw, M.D., Clinical Research Associate, Preclinical Neurosciences Section, NPB, IRP, NIMH

Dr. Darrell Kirch, Associate Clinical Associate, NPB, IRP, NIMH; Dr. William J. Freed, Chief, Preclinical Neurosciences Section, NPB, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Preclinical Neurosciences Section

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.75	.75	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 on the effects of retinoic acids on brain, behavior and drug interactions investigates the pathophysiology of retinoic acid action in vivo. Rats are the current model but expansion into mouse and guinea pig models is anticipated. The primary focus of the rat model is the assay of the pharmacokinetics of the interaction of 13-cis-retinoic acid with neuroleptics. Early results have shown statistically significant changes in the blood levels of haloperidol and one of its metabolites after the concurrent administration of 13-cis-retinoic acid to rats.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02319-01 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Localization and Characterization of Enkephalin-Containing Peptides in the Rat Gut

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Yen-Nung Wang, M.D., Visiting Associate, Neuropsychiatry Branch, IRP, NIMH

Dr. Janice Stevens, Medical Officer, Neuropsychiatry Branch, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Clinical Brain Studies

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.75	.75	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 distribution and characterization of met^5-enkephalin-arg^6-gly^7-leu^8 (met-enk-arg-gly-leu) and peptide F in the rat gastrointestinal (GI) tract was studied by immunohistochemical techniques. Antisera were found to be specific for the synthetic antigens. Met-enk-arg-gly-leu and peptide F-like immunoreactivities were found in neuronal structures in all regions of the rat GI tract. Immunoreactive somata were primarily located in the myenteric plexus; immunoreactive processes were mostly present in the myenteric plexus and the circular muscle layer. By comparing the distribution of these two peptides and other enkephalin-containing peptides (met^5-enkephalin, leu^5-enkephalin and met^5-enkephalin-arg^6-phe^7), we found that their distribution is similar. It is most likely that these five peptides coexist in the same neurons of the rat GI tract. Our results suggest that these opioid peptides may play a role in the regulation of GI functions.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02319-01 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Localization and Characterization of Enkephalin-Containing Peptides in the Rat Gut

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Yen-Nung Wang, M.D., Visiting Associate, Neuropsychiatry Branch, IRP, NIMH

Dr. Janice Stevens, Medical Officer, Neuropsychiatry Branch, IRP, NIMH; Dr. Richard Jed Wyatt, Chief, Neuropsychiatry Branch, IRP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Clinical Brain Studies

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.75	.75	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 distribution and characterization of met^5-enkephalin-arg^6-gly^7-leu^8 (met-enk-arg-gly-leu) and peptide F in the rat gastrointestinal (GI) tract was studied by immunohistochemical techniques. Antisera were found to be specific for the synthetic antigens. Met-enk-arg-gly-leu and peptide F-like immunoreactivities were found in neuronal structures in all regions of the rat GI tract. Immunoreactive somata were primarily located in the myenteric plexus; immunoreactive processes were mostly present in the myenteric plexus and the circular muscle layer. By comparing the distribution of these two peptides and other enkephalin-containing peptides (met^5-enkephalin, leu^5-enkephalin and met^5-enkephalin-arg^6-phe^7), we found that their distribution is similar. It is most likely that these five peptides coexist in the same neurons of the rat GI tract. Our results suggest that these opioid peptides may play a role in the regulation of GI functions.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02320-01 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Magnetic Resonance Imaging (MRI) Studies

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Daniel R. Weinberger, M.D., Chief, Section on Clinical Neuropsychiatry, NPB, IRP, NIMH

Dr. Jean L. Cadet, Medical Staff Fellow, Section on Clinical Neuropsychiatry, NPB, IRP, NIMH; Dr. John Kelsoe, Medical Staff Fellow, Clinical Neuroscience Branch, NIMH; Dr. David Pickar, Chief, Section on Clinical Studies, CNB, IRP, NIMH

COOPERATING UNITS *(if any)*

Clinical Neuroscience Branch, NIMH; Section on Clinical Studies, CNB

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Clinical Neuropsychiatry

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	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.)*

We are studying the neuroanatomical localization of the possible underlying pathology using MRI. Attempts will be made to correlate neuroanatomical abnormalities to other findings such as those seen in blood flow or BEAM studies.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02320-01 NPB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Magnetic Resonance Imaging (MRI) Studies

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Daniel R. Weinberger, M.D., Chief, Section on Clinical Neuropsychiatry, NPB, IRP, NIMH

Dr. Jean L. Cadet, Medical Staff Fellow, Section on Clinical Neuropsychiatry, NPB, IRP, NIMH; Dr. John Kelsoe, Medical Staff Fellow, Clinical Neuroscience Branch, NIMH; Dr. David Pickar, Chief, Section on Clinical Studies, CNB, IRP, NIMH

COOPERATING UNITS *(if any)*

Clinical Neuroscience Branch, NIMH; Section on Clinical Studies, CNB

LAB/BRANCH

Neuropsychiatry Branch

SECTION

Section on Clinical Neuropsychiatry

INSTITUTE AND LOCATION

NIMH, Saint Elizabeths Hospital, Washington, D.C.

TOTAL MAN-YEARS:	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.)*

We are studying the neuroanatomical localization of the possible underlying pathology using MRI. Attempts will be made to correlate neuroanatomical abnormalities to other findings such as those seen in blood flow or BEAM studies.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01525-10 SMRP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Regulation of Gene Expression and Protein Synthesis of Neural Tissues

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

J. P. Schwartz	Research Chemist	LPP-NIMH
H. Shinoda	Guest Researcher	LPP-NIMH

COOPERATING UNITS *(if any)*

Rabi Simantov, Salk Institute, San Diego, CA

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Molecular Biology

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.6	1.1	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.)*

Direct measurement of mRNA levels can be made using cDNA probes and one can derive an estimate of peptide turnover by measuring the precursor mRNA, the precursor and the peptide itself. Treatment of bovine adrenal chromaffin cells with 8-Br-cyclic AMP results in an increase of both proenkephalin (PE) and tyrosine hydroxylase (TH) mRNA in these cells, which is time- and dose-dependent and not replicated by 8-Br-cyclic GMP. There is a comparable change in the content of enkephalin-like peptides. Dexamethasone increases only PE mRNA and enkephalin peptides while reserpine depletes catecholamines and leads to TH induction while depleting PE mRNA and total enkephalin peptides. Depolarization by veratridine depletes enkephalins and catecholamines reapidly. PE mRNA has increased 24 hr later, a response which is enhanced by dexamethasone, whereas TH mRNA has not changed even by 48 hr.

Use of cDNA probes for PE and for proopiomelanocortin (POMC) has shown a differential distribution of the mRNAs in the CNS as well as differential regulation by such chronic drug treatments as haloperidol, reserpine, fenfluramine or 5,7-dihydroxytryptamine. Certain drugs alter peptide content by increasing biosynthesis of the mRNA whereas others act at the level of utilization.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01525-10 SMRP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Regulation of Gene Expression and Protein Synthesis of Neural Tissues

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

J. P. Schwartz	Research Chemist	LPP-NIMH
H. Shinoda	Guest Researcher	LPP-NIMH

COOPERATING UNITS *(if any)*

Rabi Simantov, Salk Institute, San Diego, CA

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Molecular Biology

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.6	1.1	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.)*

Direct measurement of mRNA levels can be made using cDNA probes and one can derive an estimate of peptide turnover by measuring the precursor mRNA, the precursor and the peptide itself. Treatment of bovine adrenal chromaffin cells with 8-Br-cyclic AMP results in an increase of both proenkephalin (PE) and tyrosine hydroxylase (TH) mRNA in these cells, which is time- and dose-dependent and not replicated by 8-Br-cyclic GMP. There is a comparable change in the content of enkephalin-like peptides. Dexamethasone increases only PE mRNA and enkephalin peptides while reserpine depletes catecholamines and leads to TH induction while depleting PE mRNA and total enkephalin peptides. Depolarization by veratridine depletes enkephalins and catecholamines reapidly. PE mRNA has increased 24 hr later, a response which is enhanced by dexamethasone, whereas TH mRNA has not changed even by 48 hr.

Use of cDNA probes for PE and for proopiomelanocortin (POMC) has shown a differential distribution of the mRNAs in the CNS as well as differential regulation by such chronic drug treatments as haloperidol, reserpine, fenfluramine or 5,7-dihydroxytryptamine. Certain drugs alter peptide content by increasing biosynthesis of the mRNA whereas others act at the level of utilization.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01531-09 SMRP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Nerve Growth Factors: Synthesis and Function

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

J. P. Schwartz Research Chemist LPP-NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Molecular Biology

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	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.)*

Recent evidence suggests that a family of nerve growth factors exist, each effective for a certain population of neurons. Mouse brain contains a factor which is NGF-like by immunoassay but has no biological activity. This factor increases in the cerebella of the pcd mutant mouse as the Purkinje cells die out and astrocytes proliferate. The mRNA for this factor appears to hybridize with mouse β-NGF cDNA and is increased in pcd cerebellum. Entorhinal cortex lesions in rat stimulate production of a factor which can be assayed by its ability to support survival of chick embryo sensory and sympathetic neurons. The mRNA for the factor can be assayed by in vitro translation in an oocyte system.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01531-09 SMRP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Nerve Growth Factors: Synthesis and Function

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

J. P. Schwartz Research Chemist LPP-NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Molecular Biology

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.5	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.)*

Recent evidence suggests that a family of nerve growth factors exist, each effective for a certain population of neurons. Mouse brain contains a factor which is NGF-like by immunoassay but has no biological activity. This factor increases in the cerebella of the pcd mutant mouse as the Purkinje cells die out and astrocytes proliferate. The mRNA for this factor appears to hybridize with mouse β-NGF cDNA and is increased in pcd cerebellum. Entorhinal cortex lesions in rat stimulate production of a factor which can be assayed by its ability to support survival of chick embryo sensory and sympathetic neurons. The mRNA for the factor can be assayed by in vitro translation in an oocyte system.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01532-09 SMRP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Regulation of Catecholamine Receptor

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

De-Maw Chuang Group Chief LPP-NIMH

COOPERATING UNITS *(if any)*

Carmine Coscia, St. Louis University Medical School
Graig Malbon, State University of New York at Stony Brook
Hannu Alho, Fidia Georgetown Neuroscience Institute

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Group of Immunochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

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 number of β-adrenergic receptor (BAR) fluctuates with changes in the neuronal activity in vivo. Two extremeties of this receptor plasticity are the supersensitivity and subsensitivity; the latter often involves the loss of receptor site, termed down-regulation. We have used a model system of frog erythrocyte to study the molecular mechanisms of β-receptor down-regulation induced by isoproterenol stimulation. Our previous studies have provided the first evidence that agonist-induced down regulation of BAR is associated with internalization of BAR sites in frog erythrocytes. This receptor internalization is causative for the desensitization of adenylate cyclase to BAR stimulation. Internalized BAR sites are sequestered in endocytotic vesicles with molecular weight more than 20×10^6 daltons and are recycled to the plasma membrane during receptor resensitization. Moreover, mechanisms of coated pit and coated vesicle may be involved in this receptor internalization and down-regulation. In the present study we have succeeded in staining BAR in frog erythrocytes using BAR specific antibody and detected important differences in the receptor staining pattern during receptor desensitization and down-regulation. Currently we are attempting to elucidate the details of molecular events at the electron microscopic level using this morphological approach. Moreover, we have investigated whether BAR internalization occurs in the CNS. Purified coated vesicles isolated from bovine brain were found to contain BAR which was uncoupled to the GTP binding protein and adenylate cyclase. These BAR sites were labeled by a liphophilic ligand ^{125}I-cyanopindolol but not by a hydrophilic ligand ^{3}H-CGP-12177. This data suggest that BAR may be internalized by coated vesicle-mechanisms in the CNS. Thus, BAR internalization might play an important role in the CNS plasticity.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01532-09 SMRP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Regulation of Catecholamine Receptor

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

De-Maw Chuang Group Chief LPP-NIMH

COOPERATING UNITS *(if any)*

Carmine Coscia, St. Louis University Medical School
Graig Malbon, State University of New York at Stony Brook
Hannu Alho, Fidia Georgetown Neuroscience Institute

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Group of Immunochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

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 number of β-adrenergic receptor (BAR) fluctuates with changes in the neuronal activity in vivo. Two extremeties of this receptor plasticity are the supersensitivity and subsensitivity; the latter often involves the loss of receptor site, termed down-regulation. We have used a model system of frog erythrocyte to study the molecular mechanisms of β-receptor down-regulation induced by isoproterenol stimulation. Our previous studies have provided the first evidence that agonist-induced down regulation of BAR is associated with internalization of BAR sites in frog erythrocytes. This receptor internalization is causative for the desensitization of adenylate cyclase to BAR stimulation. Internalized BAR sites are sequestered in endocytotic vesicles with molecular weight more than 20×10^6 daltons and are recycled to the plasma membrane during receptor resensitization. Moreover, mechanisms of coated pit and coated vesicle may be involved in this receptor internalization and down-regulation. In the present study we have succeeded in staining BAR in frog erythrocytes using BAR specific antibody and detected important differences in the receptor staining pattern during receptor desensitization and down-regulation. Currently we are attempting to elucidate the details of molecular events at the electron microscopic level using this morphological approach. Moreover, we have investigated whether BAR internalization occurs in the CNS. Purified coated vesicles isolated from bovine brain were found to contain BAR which was uncoupled to the GTP binding protein and adenylate cyclase. These BAR sites were labeled by a liphophilic ligand ^{125}I-cyanopindolol but not by a hydrophilic ligand ^{3}H-CGP-12177. This data suggest that BAR may be internalized by coated vesicle-mechanisms in the CNS. Thus, BAR internalization might play an important role in the CNS plasticity.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01555-06 SMRP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Enkephalin Metabolism

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

B. Mellstrom	Visiting Fellow	LPP-NIMH
H.-Y.T. Yang	Section Chief	LPP-NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Neuropeptide

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

TOTAL MAN-YEARS:	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 overall objective of this project is to investigate the enzymes involved in the metabolism of the met^5-enkephalin-arg^6-phe^7. Met^5-enkephalin-arg^6-phe^7 is an endogenous opioid peptide derived from preproenkephalin A. We have previously demonstrated that 1) this peptide is rapidly metabolized by an aminopeptidase and a dipeptidyl carboxypeptidase and 2) these two enzymes can be efficiently inhibited by Bestatin and Hoe 498, an angiotensin converting enzyme inhibitor. IC_{50} value of Hoe 498 diacid is 0.8 nM indicating that Hoe 498 is a highly potent inhibitor for the met^5-enkephalin-arg^6-phe^7 degradation. In this study, the specificity of Hoe 498 on the met^5-enkephalin-arg^6-phe^7 metabolism was further studied. Specifically, the effect of Hoe 498 on 1) the recoveries of met^5-enkephalin-arg^6-phe^7 and met^5-enkephalin-arg^6-gly^7-leu^8 released by 57 mM KCl from brain slices and 2) the analgesic potencies of met^5-enkephalin-arg^6-phe^7 and met^5-enkephalin-arg^6-gly^7-leu^8 were studied. In the release study, Hoe 498 protected met^5-enkephalin-arg^6-phe^7 but not met^5-enkephalin-arg^6-gly^7-leu^8. Hoe 498 potentiated the analgesic effect of intraventricularly injected met^5-enkephaln-arg^6-phe^7 but not that of met^5-enkephalin-arg^6-gly^7-leu^8.

We have previously observed that met^5-enkephalin is not protected by the dipeptidly carboxpeptidase inhibitor. This observation and the results of the present study taken together indicate that Hoe 498 can be used to prolong the half life of met^5-enkephalin-arg^6-phe^7 specifically and in turn to better study the functional role of this endogenous opioid peptide.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01555-06 SMRP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Enkephalin Metabolism

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

B. Mellstrom	Visiting Fellow	LPP-NIMH
H.-Y.T. Yang	Section Chief	LPP-NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Neuropeptide

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

TOTAL MAN-YEARS:	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 overall objective of this project is to investigate the enzymes involved in the metabolism of the met^5-enkephalin-arg^6-phe^7. Met^5-enkephalin-arg^6-phe^7 is an endogenous opioid peptide derived from preproenkephalin A. We have previously demonstrated that 1) this peptide is rapidly metabolized by an aminopeptidase and a dipeptidyl carboxypeptidase and 2) these two enzymes can be efficiently inhibited by Bestatin and Hoe 498, an angiotensin converting enzyme inhibitor. IC_{50} value of Hoe 498 diacid is 0.8 nM indicating that Hoe 498 is a highly potent inhibitor for the met^5-enkephalin-arg^6-phe^7 degradation. In this study, the specificity of Hoe 498 on the met^5-enkephalin-arg^6-phe^7 metabolism was further studied. Specifically, the effect of Hoe 498 on 1) the recoveries of met^5-enkephalin-arg^6-phe^7 and met^5-enkephalin-arg^6-gly^7-leu^8 released by 57 mM KCl from brain slices and 2) the analgesic potencies of met^5-enkephalin-arg^6-phe^7 and met^5-enkephalin-arg^6-gly^7-leu^8 were studied. In the release study, Hoe 498 protected met^5-enkephalin-arg^6-phe^7 but not met^5-enkephalin-arg^6-gly^7-leu^8. Hoe 498 potentiated the analgesic effect of intraventricularly injected met^5-enkephaln-arg^6-phe^7 but not that of met^5-enkephalin-arg^6-gly^7-leu^8.

We have previously observed that met^5-enkephalin is not protected by the dipeptidly carboxpeptidase inhibitor. This observation and the results of the present study taken together indicate that Hoe 498 can be used to prolong the half life of met^5-enkephalin-arg^6-phe^7 specifically and in turn to better study the functional role of this endogenous opioid peptide.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01559-05 SMRP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Phe-Met-Are-Phe-NH_2 Like Peptides In The Brain And Spinal Cord: Function And Distribution

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

H.-Y. T. Yang, Ph.D.	Section Chief	LPP-NIMH
E. A. Majane	Chemist	LPP-NIMH

COOPERATING UNITS *(if any)*

1) Pertti Panula, M.D., Dept. of Anatomy, University of Helsinki, Finland
2) Steve Sabol, Medical Officer, Lab. Biochem. Genet., Natl. Heart, Lung and Blood Inst.
3) Anna Maria Alho, M.D., Guest Worker, Cancer Institute

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Neuropeptide

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	0.5	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.)*

We have previously isolated and chemically characterized two putative endogenous opiate antagonist peptides. In this study, antibodies against these two peptides were produced and distribution of these two peptides in brain and spinal cord was investigated by radioimmunoassay and also immunohistochemical technique. The immunohistochemical study was carried out with the cooperation of Dr. Pertti Panula at the University of Helsinki, Finland. These two peptides were found to be unevenly distributed in the brain with the highest concentrations in dorsal spinal cord and periaqueductal gray area and the lowest levels in cortex and cerebellum. In the spinal cord, immunoreactivities were found in laminae I-II of the posterior horn. Immunohistochemically, several groups of neurons in the rat brain were immunoreactive; immunoreactive cells were found in the cerebral cortex, lateral septal nucleus, nucleus of the diagonal band, neostriatum, periventricular hypothalamic areas and several medullary nuclei.

The identification of the two putative endogenous opiate antagonist peptides in brain neurons suggest that these two peptides may have functions in neurotransmission. The enrichment of these two peptides in dorsal spinal cord and periaqueductal gray area together with our past findings led us to suggest that these two peptides may participate in pain modulation.

The proposed courses of the study on the two putative endogenous opiate antagonist peptides are: (1) to investigate the mechanism underlying the antiopiate action (2) to determine the distribution of receptors and (3) to explore the possible role of these peptides in development of opioid tolerance.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01559-05 SMRP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Phe-Met-Are-Phe-NH_2 Like Peptides In The Brain And Spinal Cord: Function And Distribution

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

H.-Y. T. Yang, Ph.D.	Section Chief	LPP-NIMH
E. A. Majane	Chemist	LPP-NIMH

COOPERATING UNITS *(if any)*

1) Pertti Panula, M.D., Dept. of Anatomy, University of Helsinki, Finland
2) Steve Sabol, Medical Officer, Lab. Biochem. Genet., Natl. Heart, Lung and Blood Inst.
3) Anna Maria Alho, M.D., Guest Worker, Cancer Institute

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Neuropeptide

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	0.5	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.)*

We have previously isolated and chemically characterized two putative endogenous opiate antagonist peptides. In this study, antibodies against these two peptides were produced and distribution of these two peptides in brain and spinal cord was investigated by radioimmunoassay and also immunohistochemical technique. The immunohistochemical study was carried out with the cooperation of Dr. Pertti Panula at the University of Helsinki, Finland. These two peptides were found to be unevenly distributed in the brain with the highest concentrations in dorsal spinal cord and periaqueductal gray area and the lowest levels in cortex and cerebellum. In the spinal cord, immunoreactivities were found in laminae I-II of the posterior horn. Immunohistochemically, several groups of neurons in the rat brain were immunoreactive; immunoreactive cells were found in the cerebral cortex, lateral septal nucleus, nucleus of the diagonal band, neostriatum, periventricular hypothalamic areas and several medullary nuclei.

The identification of the two putative endogenous opiate antagonist peptides in brain neurons suggest that these two peptides may have functions in neurotransmission. The enrichment of these two peptides in dorsal spinal cord and periaqueductal gray area together with our past findings led us to suggest that these two peptides may participate in pain modulation.

The proposed courses of the study on the two putative endogenous opiate antagonist peptides are: (1) to investigate the mechanism underlying the antiopiate action (2) to determine the distribution of receptors and (3) to explore the possible role of these peptides in development of opioid tolerance.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01577-03 SMRP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Characterization of Serotonin Pre- and Postsynaptic Components in NCB-20 Cells

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

D.-M. Chuang	Group Chief	LPP-NIMH
X.-Z. Zhu	Visiting Fellow	LPP-NIMH
T. Nakaki	Visting Fellow	LPP-NIMH
O. Dillon-Carter	Chemist	LPP-NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Immunochemistry Group

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.6	1.6	None

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.)*

NCB-20, a cloned hybrid cell line of mouse neuroblastoma and fetal Chinese hamster brain cell, has been used as a model system for the study of receptor-receptor interactions in the same cell. NCB-20 cells express 5-HT_1 receptors which are linked to adenylate cyclase; these 5-HT sensitive adenylate cyclase can be potently blocked by a 5-HT antagonist ketanserin in the low nanomolar concentration ranges. The plasma membranes of these cells also contain high affinity binding sites for ^{3}H-ketanserin and ^{3}H-mianserin. Moreover intact NCB-20 cells bind specifically ^{125}I-LSD; pharmacological characterization indicates that LSD is preferentially labeling the 5-HT_2 receptor sites. We found that these cells are also equipped with 5-HT presynaptic components. These include a 5-HT uptake system and a very high Bmax of ^{3}H-imipramine binding sites (50-times the Bmax in the CNS). We have succeeded in the solubilization of imipramine binding sites from the plasma membrane of these cells by using selective detergents and are attempting to develop useful techniques for the purification of these binding sites. It has been shown that acetylcholine is synthesized in NCB-20 cells and can be released by stimulation of 5-HT_1 receptors. We found that these cells possess muscarinic cholinergic receptors which are linked to phosphoinositide specific phospholipase C. The carbachol-induced phosphoinositide hydrolysis can be blocked by atropine and pirenzepine, a selective M_1 cholinergic receptor antagonist. The functional role of this receptor messenger is currently under investigation. In addition, we have initiated our attemp to prepare a cDNA library for the messenger RNA of NCB-20 cells in order to clone the imipramine binding sites as well as other receptor sites in these cells. This study should lead to a better understanding of molecular mechanisms of receptor regulation in a neuron.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01577-03 SMRP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

D.-M. Chuang	Group Chief	LPP-NIMH
X.-Z. Zhu	Visiting Fellow	LPP-NIMH
T. Nakaki	Visting Fellow	LPP-NIMH
O. Dillon-Carter	Chemist	LPP-NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Immunochemistry Group

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.6	1.6	None

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.)*

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01578-03 SMRP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Expression of Genes for Insulin in Brain and Peripheral Tissues

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

D.-M. Chuang	Group Chief	LPP-NIMH
T.T. Quach	Visiting Associate	NPB-NIMH
A.-M. Duchemin	Visiting Associate	NPB-NIMH

COOPERATING UNITS *(if any)*

Neuropsychiatry Branch, NIMH

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Group of Immunochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	1.2	None

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 aims of this project are to use a cDNA probe to detect the presence of mRNA for insulin or insulin-like peptide in extrapancreatic tissues including the brain and to investigate their physiological role. RNAs are extracted from various tissues using liquid nitrogen pulverization followed by homogenization in the presence of GuSCN. The RNA pellets recovered from CsCl-cushion following centrifugation of the homogenate are subjected to oligo-dt columns for the purification of poly A^+RNAs which include mRNAs. These isolated mRNAs are electrophoresed on agarose gel followed by blotting to a nitrocellulose membrane. These immobilized mRNAs are then hybridized to a cloned cDNA fragment of proinsulin gene which has been nick-translated with ^{32}P-dCTP. We found that the ^{32}P-cDNA probe is hybridized to mRNA from extrapancreatic tissues under stringent conditions (i.e., high temperature and low salts). However, the molecular sizes of these hybridizable mRNA transcripts are different from that detected in the pancreas. Thus, the size of pancreatic mRNA is of 0.5 kilobase, whereas two species of mRNA transcripts detected in the gut, heart and to a lesser extent, liver have approximately 4.2 and 2.2 kilobases. We also detected these two mRNA transcripts in the brain and a cloned cell line NCB-20 (neuroblastoma x fetal hamster brain cell hybrid), suggesting a neuronal location of these transcripts. Thus, mRNA for insulin and insulin-like can be detected in extrapancreatic tissues including the brain. Ontogenetic studies and regional distribution of these mRNAs in the brain are now in progress. Their role in the CNS awaits further investigation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01578-03 SMRP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Expression of Genes for Insulin in Brain and Peripheral Tissues

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

D.-M. Chuang	Group Chief	LPP-NIMH
T.T. Quach	Visiting Associate	NPB-NIMH
A.-M. Duchemin	Visiting Associate	NPB-NIMH

COOPERATING UNITS *(if any)*

Neuropsychiatry Branch, NIMH

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Group of Immunochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	1.2	None

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 aims of this project are to use a cDNA probe to detect the presence of mRNA for insulin or insulin-like peptide in extrapancreatic tissues including the brain and to investigate their physiological role. RNAs are extracted from various tissues using liquid nitrogen pulverization followed by homogenization in the presence of GuSCN. The RNA pellets recovered from CsCl-cushion following centrifugation of the homogenate are subjected to oligo-dt columns for the purification of poly A^+RNAs which include mRNAs. These isolated mRNAs are electrophoresed on agarose gel followed by blotting to a nitrocellulose membrane. These immobilized mRNAs are then hybridized to a cloned cDNA fragment of proinsulin gene which has been nick-translated with ^{32}P-dCTP. We found that the ^{32}P-cDNA probe is hybridized to mRNA from extrapancreatic tissues under stringent conditions (i.e., high temperature and low salts). However, the molecular sizes of these hybridizable mRNA transcripts are different from that detected in the pancreas. Thus, the size of pancreatic mRNA is of 0.5 kilobase, whereas two species of mRNA transcripts detected in the gut, heart and to a lesser extent, liver have approximately 4.2 and 2.2 kilobases. We also detected these two mRNA transcripts in the brain and a cloned cell line NCB-20 (neuroblastoma x fetal hamster brain cell hybrid), suggesting a neuronal location of these transcripts. Thus, mRNA for insulin and insulin-like can be detected in extrapancreatic tissues including the brain. Ontogenetic studies and regional distribution of these mRNAs in the brain are now in progress. Their role in the CNS awaits further investigation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01579-03 SMRP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Studies of an endogenous ligand for the 5HT$_2$ recognition site

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

B.L. Roth	Guest Researcher	LPP-NIMH
D.-M. Chuang	Chemist	LPP-NIMH
X.-Z. Zhu	Visiting Fellow	LPP-NIMH

COOPERATING UNITS *(if any)*

S. McLean, Lab. Neurophysiology, NIMH
B.L. Roth, Naval Medical Research Institute

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Immunochemistry Group

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	0

CHECK APPROPRIATE BOX(ES)

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

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

5-HT$_2$ receptors have low affinity for serotonin (5-HT) and do not show receptor supersensitivity following lesion of nerve ending. We have proposed for the existence of an endogenous ligand (endocoid) for this receptor site. Our previous studies have demonstrated that some protein fractions derived from bovine and rat brains display activity of inhibiting ^{3}H-ketanserin binding but inhibiting only slightly ^{3}H-mianserin binding to rat brain membrane. This protein (Mr=6000) has been partially purified by gel filtration and HPLC column chromatography. The present report shows that rat brain striatum contained an unique ^{3}H -ketanserin recognition site which was insensitive to mianserin and could be the receptor site for this putative endocoid. Radioligand binding assays disclosed high and low affinity ketanserin binding sites in the rat striatum. Only the high affinity sites were inhibited with nanomolar affinity by classical 5-HT$_2$ antagonist and showed up-regulation by chronic p-chloro-phenylalanine treatment. Autoradiographic studies showed that mianserin (100 nM) displaced only the binding of ^{3}H-ketanserin to the cortex and septum but not that to the striatum. Perhaps these mianserin-resistent ketanserin sites represent the receptor for this or some yet undiscovered peptide. The present finding might have clinical implication for the etiology of affective disorders.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01579-03 SMRP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Studies of an enogcoid for the $5HT_2$ recognition site

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

B.L. Roth	Guest Researcher	LPP-NIMH
D.-M. Chuang	Chemist	LPP-NIMH
X.-Z. Zhu	Visiting Fellow	LPP-NIMH

COOPERATING UNITS *(if any)*

S. McLean, Lab. Neurophysiology, NIMH
B.L. Roth, Naval Medical Research Institute

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Immunochemistry Group

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	0

CHECK APPROPRIATE BOX(ES)

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

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

$5HT_2$ receptors have low affinity for serotonin (5-HT) and do not show receptor supersensitivity following lesion of nerve ending. We have proposed for the existence of an endogenous ligand (endocoid) for this receptor site. Our previous studies have demonstrated that some protein fractions derived from bovine and rat brains display activity of inhibiting ^{3}H-ketanserin binding but inhibiting only slightly ^{3}H-mianserin binding to rat brain membrane. This protein (Mr=6000) has been partially purified by gel filtration and HPLC column chromatography. The present report shows that rat brain striatum contained an unique ^{3}H -ketanserin recognition site which was insensitive to mianserin and could be the receptor site for this putative endocoid. Radioligand binding assays disclosed high and low affinity ketanserin binding sites in the rat striatum. Only the high affinity sites were inhibited with nanomolar affinity by classical $5\text{-}HT_2$ antagonist and showed up-regulation by chronic p-chloro-phenylalanine treatment. Autoradiographic studies showed that mianserin (100 nM) displaced only the binding of ^{3}H-ketanserin to the cortex and septum but not that to the striatum. Perhaps these mianserin-resistent ketanserin sites represent the receptor for this or some yet undiscovered peptide. The present finding might have clinical implication for the etiology of affective disorders.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01584-03 SMRP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Noncompetitive Interactions Between Mu- and Delta-Opiate Receptors In Vitro

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Richard B. Rothman	Guest Researcher	LPP-NIMH
M. Herkenham	Staff Scientist	LNP-NIMH
S. McLean	Staff Fellow	LNP-NIMH
J. Cadet	Staff Scientist	NPB-NIMH
J. Byrd	Guest Researcher	LPP-NIMH
K. Rice	Staff Scientist	LC-NIADDKD
V. Bykov	Student Volunteer	LPP-NIMH

COOPERATING UNITS *(if any)*

B. Roth, Naval Medical Research Institute, Bethesda, MD
J. Holaday, Walter Reed Army Institute for Research, Washington, D.C.

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Neuropeptide

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

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 in my laboratory is directed towards testing a model of the opioid receptors sufficiently complex enough to explain varied physiological data. This model postuates a receptor complex consisting of adjacent and interacting mu, delta and kappa binding sites, as well as distinct mu, delta and kappa receptors not associated with the receptor complex.

To test this model we utilize several techniques: (1) quantitative ligand binding studies using the method of "binding surface analysis" and weighted nonlinear least squares curve fitting, (2) site-directed alkylating agents such as BIT (mu-directed), FIT (delta-directed) and beta-FNA (mu-directed), (3) receptor autoradiography to provide anatomical information, (4) "in vivo" manipulations such as chronic morphine and chronic naltrexone which up-regulate opiate receptors and (5) biochemical information using a technique to cross-link ^{125}I-beta endorphin to opiate receptors.

As our work progress, not only is the model tested, but additional data is generated. Our work addresses fundamental issues of morphine tolerance and dependence. It has defined the opiate receptors labeled by (^{3}H) cycloFOXY, a novel antagonist suitable for position emission tomography. We have developed methods for measuring rat brain kappa receptors, a subtype of the opiate receptor implicated in eating disorders and work is underway to develop a kappa-directed site-directed alkylating agent.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01584-03 SMRP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

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PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Richard B. Rothman	Guest Researcher	LPP-NIMH
M. Herkenham	Staff Scientist	LNP-NIMH
S. McLean	Staff Fellow	LNP-NIMH
J. Cadet	Staff Scientist	NPB-NIMH
J. Byrd	Guest Researcher	LPP-NIMH
K. Rice	Staff Scientist	LC-NIADDKD
V. Bykov	Student Volunteer	LPP-NIMH

COOPERATING UNITS *(if any)*

B. Roth, Naval Medical Research Institute, Bethesda, MD
J. Holaday, Walter Reed Army Institute for Research, Washington, D.C.

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Neuropeptide

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

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 in my laboratory is directed towards testing a model of the opioid receptors sufficiently complex enough to explain varied physiological data. This model postuates a receptor complex consisting of adjacent and interacting mu, delta and kappa binding sites, as well as distinct mu, delta and kappa receptors not associated with the receptor complex.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01585-02 SMRP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Molecular Mechanisms of Smooth Muscle Cell Contraction in Rat Aorta

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

B.L. Roth	Guest Researcher	LPP, NIMH
T. Nakaki	Visiting Fellow	LPP, NIMH
D.-M. Chuang	Group Chief	LPP, NIMH

COOPERATING UNITS *(if any)*

Naval Medical Research Institute, Surgical Res. Br., Bethesda, MD

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Group of Immunochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.4	1.4	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 smooth muscle of rat aorta was used as a model for the study of the molecular mechanisms of 5-HT_2 receptor function. We have previously shown that 5-HT receptors in rat aorta are coupled to phosphoinositide (PI) - specific phospholipase C. Further, we showed that the mechanism of contraction elicited by 5-HT is a complicated scenario involving receptor-mediated activation of calcium channels and a phospholipase C. We now report that in rat aorta, the 5-HT-induced contraction and PI turnover are modulated by biologically active phorbol esters. In rat aorta the 5-HT-induced contraction and PI hydrolysis (EC_{50}=10±3 uM) were highly correlated. Also, the inhibitory potency of a variety of 5-HT_2 antagonists was correlated with binding to the brain 5-HT_2 receptor. Further, the tumor-promoting phorbol ester, phorbol dibutyrate (PDB), inhibited 5-HT-induced PI turnover at low nM concentrations, while the biologically inactive substance 4-α-phorbol was ineffective. Pretreatment of aortic rings with PDB at concentrations which densensitized 5-HT-induced PI turnover also attenuated the aortic contraction induced by 5-HT in the presence of a calcium channel blocker, nitrendipine. Our results suggest that phorbol esters desensitize 5-HT receptor-mediated PI turnover and contraction, probably by activation of protein kinase C. Studies of the physiological substrates for protein kinase C in aorta smooth cells are now in progress.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01585-02 SMRP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Molecular Mechanisms of Smooth Muscle Cell Contraction in Rat Aorta

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

B.L. Roth	Guest Researcher	LPP, NIMH
T. Nakaki	Visiting Fellow	LPP, NIMH
D.-M. Chuang	Group Chief	LPP, NIMH

COOPERATING UNITS *(if any)*

Naval Medical Research Institute, Surgical Res. Br., Bethesda, MD

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Group of Immunochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.4	1.4	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 smooth muscle of rat aorta was used as a model for the study of the molecular mechanisms of 5-HT_2 receptor function. We have previously shown that 5-HT receptors in rat aorta are coupled to phosphoinositide (PI) - specific phospholipase C. Further, we showed that the mechanism of contraction elicited by 5-HT is a complicated scenario involving receptor-mediated activation of calcium channels and a phospholipase C. We now report that in rat aorta, the 5-HT-induced contraction and PI turnover are modulated by biologically active phorbol esters. In rat aorta the 5-HT-induced contraction and PI hydrolysis (EC_{50}=10±3 uM) were highly correlated. Also, the inhibitory potency of a variety of 5-HT_2 antagonists was correlated with binding to the brain 5-HT_2 receptor. Further, the tumor-promoting phorbol ester, phorbol dibutyrate (PDB), inhibited 5-HT-induced PI turnover at low nM concentrations, while the biologically inactive substance 4-α-phorbol was ineffective. Pretreatment of aortic rings with PDB at concentrations which densensitized 5-HT-induced PI turnover also attenuated the aortic contraction induced by 5-HT in the presence of a calcium channel blocker, nitrendipine. Our results suggest that phorbol esters desensitize 5-HT receptor-mediated PI turnover and contraction, probably by activation of protein kinase C. Studies of the physiological substrates for protein kinase C in aorta smooth cells are now in progress.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02298-01 SMRP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Receptor Regulation in Cultured Cerebellum Granule Cells

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Jian Xu	Visiting Fellow	LPP-NIMH
De-Maw Chuang	Group Chief	LPP-NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Group of Immunochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	1.2	0

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

The present study shows that cerebellar granule cells contain receptors for serotonin (5-HT), acetylcholine and norepinephrine and that these receptors are coupled to phosphoinositide hydrolysis, resulting in the accumulation of inositol monophosphate (IP_1) in the presence of lithium. 5-HT increased the IP_1 accumulatin with an EC_{50} of 10^{-7}M and a saturation concentration of 10^{-5}M. The maximal activation was about 700% of the control which was much greater than that seen in brain slices of mature rats. Studies with various agonists and antagonists indicated that this 5-HT response was mainly mediated by 5-HT_2 receptors. Carbachol dramatically increased IP_1 accumulation by about 30-fold with an EC_{50} of approximately 10 μM. This effect could be potently blocked by atropine and pirenzepine, suggesting that this may be a M_1 receptor-mediated event. Pretreatment of cells with carbachol for more than 1 hr resulted in the desensitization of the carbachol effect on IP_1 accumulation and the loss of receptor binding assessed by ^{3}H-QNB. The carbachol-induced response on phosphoinositide turnover could be partially attenuated by biologically active phorbol esters, whereas the biologically inactive phorbol had no apparent effect. Neither the carbachol nor the 5-HT-induced response was affected by pretreatment with a pertussis toxin. Norepinephrine also increased IP_1 accumulation by more than 300% with an EC_{50} of about 2 μM; this activation was potently blocked by prazosin, an α_1 receptor antagonist. Granule cells in the primary culture is a useful model for the study of receptor regulation in the CNS.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02298-01 SMRP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Receptor Regulation in Cultured Cerebellum Granule Cells

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Jian Xu	Visiting Fellow	LPP-NIMH
De-Maw Chuang	Group Chief	LPP-NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Group of Immunochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	1.2	0

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

The present study shows that cerebellar granule cells contain receptors for serotonin (5-HT), acetylcholine and norepinephrine and that these receptors are coupled to phosphoinositide hydrolysis, resulting in the accumulation of inositol monophosphate (IP_1) in the presence of lithium. 5-HT increased the IP_1 accumulatin with an EC_{50} of 10^{-7}M and a saturation concentration of 10^{-5}M. The maximal activation was about 700% of the control which was much greater than that seen in brain slices of mature rats. Studies with various agonists and antagonists indicated that this 5-HT response was mainly mediated by 5-HT_2 receptors. Carbachol dramatically increased IP_1 accumulation by about 30-fold with an EC_{50} of approximately 10 μM. This effect could be potently blocked by atropine and pirenzepine, suggesting that this may be a M_1 receptor-mediated event. Pretreatment of cells with carbachol for more than 1 hr resulted in the desensitization of the carbachol effect on IP_1 accumulation and the loss of receptor binding assessed by ^{3}H-QNB. The carbachol-induced response on phosphoinositide turnover could be partially attenuated by biologically active phorbol esters, whereas the biologically inactive phorbol had no apparent effect. Neither the carbachol nor the 5-HT-induced response was affected by pretreatment with a pertussis toxin. Norepinephrine also increased IP_1 accumulation by more than 300% with an EC_{50} of about 2 μM; this activation was potently blocked by prazosin, an α_1 receptor antagonist. Granule cells in the primary culture is a useful model for the study of receptor regulation in the CNS.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02299-01 SMRP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Receptor-Mediated Phosphoinositide Turnover

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

De-maw Chuang	Group Chief	LPP-NIMH
Ora Dillon-Carter	Chemist	LPP-NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Immunochemistry Group

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	1.2	None

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 aims at the role and regulation of receptor-coupled phospholipase C. We found that in a clonal neurotumor hybrid NCB-20, these cells expresses a variety of receptors of neurotransmitters and neuromodulators that are coupled to phosphoinositide (PI) hydrolysis. Carbachol, a muscarinic cholinergic receptor agonist markedly increased the accumulation of inositol monophosphate (IP_1) in the presence of lithium (Li^+). This increase was time and dose dependent. The formation of inositol bisphosphate and trisphosphate were also increased by this agonist but to a lesser extent and with a faster time course. Antagonist specificity suggests that this effect is mediated by the M_1 cholinergic receptor. This activation is associated with a rapid increase in the efflux of ^{45}Ca from cells. Carbachol-induced IP_1 accumulation can be attenuated by pretreatment of cells with biologically active phorbol esters, suggesting a possible feedback regulation by protein kinase C activation. NCB-20 cells also contain histamine-sensitive PI turnover system. Antagonist effect indicated that this is a histamine H_1 receptor-mediated response. Neuropeptides, bradykinin, angiotensin II and neurotensin, all caused a dose-dependent activation of IP_1 accumulation. Moreover, the effects of these three peptides were non-additive, suggesting that a common or convergent mechanism may be involved in this activation. In contrast, the effect of carbachol was additive with regard to those induced by these neuropeptides. We also found that NCB-20 cells express an unusual form of inositol 1-phosphatase which is about 10 time less sensitive to Li^+. This finding might lead to some clinical implication for the therapeutic effect of Li^+ for manic depression patients.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02299-01 SMRP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Receptor-Mediated Phosphoinositide Turnover

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

De-maw Chuang	Group Chief	LPP-NIMH
Ora Dillon-Carter	Chemist	LPP-NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Immunochemistry Group

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	1.2	None

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 aims at the role and regulation of receptor-coupled phospholipase C. We found that in a clonal neurotumor hybrid NCB-20, these cells expresses a variety of receptors of neurotransmitters and neuromodulators that are coupled to phosphoinositide (PI) hydrolysis. Carbachol, a muscarinic cholinergic receptor agonist markedly increased the accumulation of inositol monophosphate (IP_1) in the presence of lithium (Li^+). This increase was time and dose dependent. The formation of inositol bisphosphate and trisphosphate were also increased by this agonist but to a lesser extent and with a faster time course. Antagonist specificity suggests that this effect is mediated by the M_1 cholinergic receptor. This activation is associated with a rapid increase in the efflux of ^{45}Ca from cells. Carbachol-induced IP_1 accumulation can be attenuated by pretreatment of cells with biologically active phorbol esters, suggesting a possible feedback regulation by protein kinase C activation. NCB-20 cells also contain histamine-sensitive PI turnover system. Antagonist effect indicated that this is a histamine H_1 receptor-mediated response. Neuropeptides, bradykinin, angiotensin II and neurotensin, all caused a dose-dependent activation of IP_1 accumulation. Moreover, the effects of these three peptides were non-additive, suggesting that a common or convergent mechanism may be involved in this activation. In contrast, the effect of carbachol was additive with regard to those induced by these neuropeptides. We also found that NCB-20 cells express an unusual form of inositol 1-phosphatase which is about 10 time less sensitive to Li^+. This finding might lead to some clinical implication for the therapeutic effect of Li^+ for manic depression patients.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02300-01 SMRP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Regulation of neurotransmitter receptors by cell differentiation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Xing-Zu Zhu	Visiting Fellow	LPP-NIMH
De-Maw Chuang	Group Chief	LPP-NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Immunochemistry Group

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	1.2	None

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 Understanding of the molecular mechanisms of the differentiation of neurons during development is of fundamental importance in neuroscience. We have used a neuronal hybridoma, NCB-20, to study the receptor regulation induced by two differentiation promoters, dibutyryl cAMP (dBcAMP) and butyrate. Exposure of cells to dBcAMP caused a time and dose dependent decrease in the binding to receptors of muscarinic acetylcholine, adrenergic α_2 and opioid δ. In the presence of 50 μM 3-isobutylmethylxanthine (IBMX), the EC_{50} of dBcAMP for inducing these decrease was about 0.14 mM and the maximal effects were seen after 48-72 hrs exposure. These down-regulation was associated with morphological changes characteristic for differentiation. The loss of muscarinic cholinergic receptor site assessed by using ^{3}H-QNB as the binding was about 40% of the control; this decrease was associated with an attenuation of the carbachol-induced phosphoinositide hydrolysis. The maximal decreases of adrenergic α_2 and opioid δ receptor binding were 20% and 80% respectively when ^{3}H-clonidine and ^{3}H-D-ala-D-leu-enkephalin were used as their respective ligands. In contrast, butyrate induced a time and dose dependent increase in the opioid receptor binding. The maximal increase was about 300% of the control when 1 mM of butyrate was added to the culture for 72 hrs. Scatchard analysis indicated that this effect was mainly due to an increase in the receptor density in the plasma membrane. This effect appeared to be relatively specific for opioid receptor because similar treatments increased only slightly (25%) the binding of ^{3}H-QNB and failed to affect the binding of ^{3}H-clonidine. Butyrate treatment induced cell morphological changes which were distinct from those induced by dBcAMP. These results imply that differentiation of neurons promoted by different agents may involved either the disappearance of old messenger RNA or induction of new messenger RNA for the receptor protein.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02300-01 SMRP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Regulation of neurotransmitter receptors by cell differentiation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Xing-Zu Zhu	Visiting Fellow	LPP-NIMH
De-Maw Chuang	Group Chief	LPP-NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Immunochemistry Group

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	1.2	None

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 Understanding of the molecular mechanisms of the differentiation of neurons during development is of fundamental importance in neuroscience. We have used a neuronal hybridoma, NCB-20, to study the receptor regulation induced by two differentiation promoters, dibutyryl cAMP (dBcAMP) and butyrate. Exposure of cells to dBcAMP caused a time and dose dependent decrease in the binding to receptors of muscarinic acetylcholine, adrenergic α_2 and opioid δ. In the presence of 50 μM 3-isobutylmethylxanthine (IBMX), the EC_{50} of dBcAMP for inducing these decrease was about 0.14 mM and the maximal effects were seen after 48-72 hrs exposure. These down-regulation was associated with morphological changes characteristic for differentiation. The loss of muscarinic cholinergic receptor site assessed by using ^{3}H-QNB as the binding was about 40% of the control; this decrease was associated with an attenuation of the carbachol-induced phosphoinositide hydrolysis. The maximal decreases of adrenergic α_2 and opioid δ receptor binding were 20% and 80% respectively when ^{3}H-clonidine and ^{3}H-D-ala-D-leu-enkephalin were used as their respective ligands. In contrast, butyrate induced a time and dose dependent increase in the opioid receptor binding. The maximal increase was about 300% of the control when 1 mM of butyrate was added to the culture for 72 hrs. Scatchard analysis indicated that this effect was mainly due to an increase in the receptor density in the plasma membrane. This effect appeared to be relatively specific for opioid receptor because similar treatments increased only slightly (25%) the binding of ^{3}H-QNB and failed to affect the binding of ^{3}H-clonidine. Butyrate treatment induced cell morphological changes which were distinct from those induced by dBcAMP. These results imply that differentiation of neurons promoted by different agents may involved either the disappearance of old messenger RNA or induction of new messenger RNA for the receptor protein.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02301-01 SMRP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Functional Role of Adrenal NPY

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

H.-Y. T. Yang,	Section Chief	LPP-NIMH
E.A. Majane	Chemist	LPP-NIMH

COOPERATING UNITS *(if any)*

Terry D. Hexum, Ph.D., Associate Prof., Dept. of Pharmacology, University of Nebraska, Medical Center, Omaha, Nebraska

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Laboratory of Preclinical Pharmacology

SECTION

Neuropeptide

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NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

TOTAL MAN-YEARS:	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.)*

NPY exists in high quantity in adrenal glands of various species. In order to explore the role of NPY in the adrenal function we have studied (1) the cellular location of NPY in the bovine adrenal gland (2) the secretion and regulation of the adrenal NPY and (3) the possible role of NPY on the catecholamine secretion.

In bovine adrenal glands, NPY was found to be stored in granules in norepinephrine containing chromaffin cells and also in nerve fibers crossing through cortex and medulla. The NPY content in adrenal glands of rats increases markedly with age during maturation and this increase is dependent on splanchnic nerve activity. In the older rat, in addition to the very large increase in the quantity, another molecular form of NPY was detected. This unidentified NPY-like peptide has been determined to be not a metabolite of the authentic NPY. Release of NPY from adrenal glands was studied using retrogradely perfused bovine adrenal glands. Release of NPY was induced by perfusing the glands with acetylcholine and this effect was antagonized by hexamethonium. The results suggest that NPY secretion is mediated by the activation of cholinergic nicotinic receptor. Effect of NPY on catecholamine release was investigated using cultured chromaffin cells. NPY at low concentrations (1 nM to 200 nM) inhibited the nicotine induced release of both norepinephrine and epinephrine in a concentration dependent manner. The results taken together suggest that NPY is released via activation of the cholinergic nicotinic receptor from chromaffin cells and then act as a physiological inhibitory modulator on the adrenal function such as catecholamine secretion. The marked age dependent increase of adrenal NPY and appearance of another form of NPY-like peptide in older rats suggest that NPY may be an interesting area for studying aging. The proposed courses of this study are (1) to investigate molecular mechanism underlying the inhibitory action of NPY in catecholamine release, (2) to chemically and biologically characterize the NPY-like peptide which appears in adrenal glands of older rats and (3) to determine whether the age dependent increase of NPY also occurs in human adrenal glands.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02301-01 SMRP

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Functional Role of Adrenal NPY

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

H.-Y. T. Yang,	Section Chief	LPP-NIMH
E.A. Majane	Chemist	LPP-NIMH

COOPERATING UNITS *(if any)*

Terry D. Hexum, Ph.D., Associate Prof., Dept. of Pharmacology, University of Nebraska, Medical Center, Omaha, Nebraska

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Neuropeptide

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	0.5	1.0

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

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

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02305-01 SMRP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Neural Crest Differentiation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

J.C. Byrd	Guest Researcher	LPP-NIMH
Ulrike Lichti	Staff Scientist	DCCP-NCI

COOPERATING UNITS *(if any)*

Hannu Alho, Fidia-Georgetown Institute for the Neurosciences, Wash., D.C. 20007
Iris Lindberg, Louisiana State University Medical Center, New Orleans, LA 70112
Jose R. Naranjo, Fidia-Georgetown Institute for the Neurosciences, Wash., D.C. 20007

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Group of Immunochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

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.)*

PC12 cells were used as a model system to study neural crest differentiation. These cells respond to nerve growth factor (NGF) by differentiating into sympathetic-like neurons. We have investigated the effects of another differentiation promotor, sodium butyrate, on PC12 cells. We have found that sodium butyrate causes PC12 cells to differentiate into APUD-like cells, which resemble chromaffin cells in several respects. Butyrate-induced changes include the following: cessation of cellular proliferation, increased cell adhesion, synthesis of neuron -specific enolase, expression of proenkephalin mRNA and its gene products, and the synthesis of tissue transglutaminase. We are continuing to investigate the mechanisms by which sodium butyrate promotes differentiation in PC12 cells.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02305-01 SMRP

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October 1, 1985 through September 30, 1986

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

Neural Crest Differentiation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

J.C. Byrd	Guest Researcher	LPP-NIMH
Ulrike Lichti	Staff Scientist	DCCP-NCI

COOPERATING UNITS *(if any)*

Hannu Alho, Fidia-Georgetown Institute for the Neurosciences, Wash., D.C. 20007
Iris Lindberg, Louisiana State University Medical Center, New Orleans, LA 70112
Jose R. Naranjo, Fidia-Georgetown Institute for the Neurosciences, Wash., D.C. 20007

LAB/BRANCH

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SECTION

Group of Immunochemistry

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

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☐ (a1) Minors

☐ (a2) Interviews

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

PC12 cells were used as a model system to study neural crest differentiation. These cells respond to nerve growth factor (NGF) by differentiating into sympathetic-like neurons. We have investigated the effects of another differentiation promotor, sodium butyrate, on PC12 cells. We have found that sodium butyrate causes PC12 cells to differentiate into APUD-like cells, which resemble chromaffin cells in several respects. Butyrate-induced changes include the following: cessation of cellular proliferation, increased cell adhesion, synthesis of neuron -specific enolase, expression of proenkephalin mRNA and its gene products, and the synthesis of tissue transglutaminase. We are continuing to investigate the mechanisms by which sodium butyrate promotes differentiation in PC12 cells.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02306-01 SMRP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Epinephrine Synthesis and Methyltransferase Activity in PC12 Cells

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

J. C. Byrd	Guest Researcher	LPP-NIMH
M. Hadjiconstantinou	Guest Researcher	LPP-NIMH
J. Cadet	Staff Scientist	NPB-NIMH
D. Cavalla	Visiting Fellow	LPP-NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Immunochemistry Group

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

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 shown that PC12 cells synthesize epinephrine, that dexamethasone increases their epinephrine content, and that PNMT (phenylethanolamine-N-methyltransferase) activity is increased following dexamethasone treatment. In addition, to PNMT, PC12 cells contain other non-specific methyltransferases. These enzymes may be involved in the generation of neurotoxic compounds (e.g. MPTP) from naturally - occurring phenylpyridines.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02306-01 SMRP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

J. C. Byrd	Guest Researcher	LPP-NIMH
M. Hadjiconstantinou	Guest Researcher	LPP-NIMH
J. Cadet	Staff Scientist	NPB-NIMH
D. Cavalla	Visiting Fellow	LPP-NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Preclinical Pharmacology

SECTION

Immunochemistry Group

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Saint Elizabeths Hospital, Washington, D.C. 20032

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

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 shown that PC12 cells synthesize epinephrine, that dexamethasone increases their epinephrine content, and that PNMT (phenylethanolamine-N-methyltransferase) activity is increased following dexamethasone treatment. In addition, to PNMT, PC12 cells contain other non-specific methyltransferases. These enzymes may be involved in the generation of neurotoxic compounds (e.g. MPTP) from naturally - occurring phenylpyridines.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02152-07

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Discipline and Parental Control in Families with Affective Disorders

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	G. Kochanska	Senior Staff Fellow	LDP NIMH
OTHER:	L. Kuczynski	Assoc. Professor of Psychology	Univ. Of Guelph Guelph, Ontario
	M. Radke-Yarrow	Chief	LDP NIMH

COOPERATING UNITS *(if any)*

University of Guelph
Guelph, Ontario, Canada

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MANYEARS: Person Years	PROFESSIONAL:	OTHER:
1.50	.80	.70

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.)*

Mothers' discipline and control practices and their children's responses to maternal control attempts are studied in well and clinically depressed mothers. Impaired parental skills in managing children's behavior have often been implied in the etiology of maladaptive patterns of child development. Depressive symptomatology, on the other hand, has been linked to inappropriate control practices, but specific difficulties of depressed mothers and possible implications for their children's development have not been identified. Assessments of mother and child behavior are based on observations of their interaction in a naturalistic setting (see Annual Report MH 02144). Detailed measures of maternal control were taken, including goals, timing and specific techniques, and the overall interactive quality of control episodes. Child response was also measured in terms of compliance to maternal demands and in terms of level of social competence of noncompliance strategies. Analyses revealed that severity of maternal affective illness results in specific inappropriate and maladaptive patterns of maternal control interventions. Children of normal mothers, but not of depressed mothers become more cooperative over time. In particular, daughters of depressed mothers appeared at risk for noncompliance problems. Maternal illness was also found to impair toddlers ability to negotiate competently with their mothers.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02152-07

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

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PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	G. Kochanska	Senior Staff Fellow	LDP NIMH
OTHER:	L. Kuczynski	Assoc. Professor of Psychology	Univ. Of Guelph Guelph, Ontario
	M. Radke-Yarrow	Chief	LDP NIMH

COOPERATING UNITS *(if any)*

University of Guelph
Guelph, Ontario, Canada

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MANYEARS: Person Years	PROFESSIONAL:	OTHER:
1.50	.80	.70

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.)*

Mothers' discipline and control practices and their children's responses to maternal control attempts are studied in well and clinically depressed mothers. Impaired parental skills in managing children's behavior have often been implied in the etiology of maladaptive patterns of child development. Depressive symptomatology, on the other hand, has been linked to inappropriate control practices, but specific difficulties of depressed mothers and possible implications for their children's development have not been identified. Assessments of mother and child behavior are based on observations of their interaction in a naturalistic setting (see Annual Report MH 02144). Detailed measures of maternal control were taken, including goals, timing and specific techniques, and the overall interactive quality of control episodes. Child response was also measured in terms of compliance to maternal demands and in terms of level of social competence of noncompliance strategies. Analyses revealed that severity of maternal affective illness results in specific inappropriate and maladaptive patterns of maternal control interventions. Children of normal mothers, but not of depressed mothers become more cooperative over time. In particular, daughters of depressed mothers appeared at risk for noncompliance problems. Maternal illness was also found to impair toddlers ability to negotiate competently with their mothers.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02156-07 LDP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Personality Development of Children Reared by Normal and Depressed Mothers

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	F. Bridges-Cline	Guest Researcher	LDP NIMH
OTHER:	G. Kochanska	Senior Staff Fellow	LDP NIMH
	M. Radke-Yarrow	Chief	LDP NIMH

COOPERATING UNITS *(if any)*

NONE

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS: Person Years	PROFESSIONAL:	OTHER:
1.00	.95	.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 focuses on the role of early childhood inhibition in the development of pathological risk indicators in children of families with and without parental depression. Patterns of child behavior in the face of the unfamiliar (persons, places), such as behaviors expressing inhibited exploratory activity and social withdrawal are observed at 2 to 3 years of age and again, at 5 to 6 years of age in semi-naturalistic but standard settings, which represent varied contexts of unfamiliarity. Preliminary analyses of the data from the earlier period of measurement (2-3 years of age) revealed that four reliable dimensions of response styles could be empirically derived from our observation coding system, which meaningfully distinguish groups of children in our sample at this very young age. Comparisons of these four dimensions of early behavioral inhibition across maternal diagnostic groups of normal, major depressive and bipolar indicate that the young children of the major depressive mothers in our sample typically exhibit the most inhibited forms of these response characteristics. The children of the Bipolar mothers typically exhibit the most active and independent forms of response when the situation is that of an unfamiliar environment. However, in the situation of an unfamilar person, the children of the Bipolar mothers, as a group, exhibit very divergent forms of response to this kind of environmental challenge, scoring at both the inhibited and uninhibited polar extremes of the response scales. Longitudinal data are being analyzed to examine the direct and indirect associations of these early response characteristics of inhibition with later manifestations of disordered or healthy behavior at 5-6 years.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02156-07 LDP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Personality Development of Children Reared by Normal and Depressed Mothers

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	F. Bridges-Cline	Guest Researcher	LDP NIMH
OTHER:	G. Kochanska	Senior Staff Fellow	LDP NIMH
	M. Radke-Yarrow	Chief	LDP NIMH

COOPERATING UNITS *(if any)*

NONE

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS: Person Years	PROFESSIONAL:	OTHER:
1.00	.95	.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 focuses on the role of early childhood inhibition in the development of pathological risk indicators in children of families with and without parental depression. Patterns of child behavior in the face of the unfamiliar (persons, places), such as behaviors expressing inhibited exploratory activity and social withdrawal are observed at 2 to 3 years of age and again, at 5 to 6 years of age in semi-naturalistic but standard settings, which represent varied contexts of unfamiliarity. Preliminary analyses of the data from the earlier period of measurement (2-3 years of age) revealed that four reliable dimensions of response styles could be empirically derived from our observation coding system, which meaningfully distinguish groups of children in our sample at this very young age. Comparisons of these four dimensions of early behavioral inhibition across maternal diagnostic groups of normal, major depressive and bipolar indicate that the young children of the major depressive mothers in our sample typically exhibit the most inhibited forms of these response characteristics. The children of the Bipolar mothers typically exhibit the most active and independent forms of response when the situation is that of an unfamiliar environment. However, in the situation of an unfamilar person, the children of the Bipolar mothers, as a group, exhibit very divergent forms of response to this kind of environmental challenge, scoring at both the inhibited and uninhibited polar extremes of the response scales. Longitudinal data are being analyzed to examine the direct and indirect associations of these early response characteristics of inhibition with later manifestations of disordered or healthy behavior at 5-6 years.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02164-06 LDP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

The Impact of Biological Changes on Psychological Functioning During Adolescence

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	E.J. Susman	Guest Researcher	LDP NIMH
OTHER:	E.D. Nottelmann	Research Psychologist	LDP NIMH
	G.I. Germain	Research Psychologist	LDP NIMH
	L.D. Dorn	Guest Researcher	LDP NIMH
	G.P. Chrousos	Senior Investigator	DEB NICHD
	G.B. Cutler	Senior Investigator	DEB NICHD
	D.L. Loriaux	Chief	DEB NICHD

COOPERATING UNITS *(if any)*

Developmental Endocrinology, NICHD

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS: Person Years	PROFESSIONAL:	OTHER:
2.92	1.07	1.85

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.)*

Interrelations of adolescents' psychological functioning and endocrine and physical growth variables are investigated. Participants are 56 boys and 52 girls, 9 to 14 years old, and their parents. Participants were evaluated on biological and psychological variables at three times of measurement, six months apart. Biological measures include stage of pubertal development (Tanner stage), assessed by a physical examination, and hormone levels, assessed by serum levels of gonadotropins, gonadal steroids, adrenal androgens, and cortisol. Psychological measures include assessments of behavior problems, affective states, interpersonal functioning, parent-child interactions in standard laboratory situations, and cognitive functioning. Relations between hormone levels and anxiety and depressive symptoms, parent-child interactions, and cognitive functioning were examined. Hormone levels of boys, primarily gonadal steroids and adrenal androgens, were predictive of anxiety and depressive symptoms one year later. Hormone levels, per se, were not predictive of anxiety and depressive symptoms one year later in girls. A more rapid rate of change (across one year) in level of adrenal androgens in boys and gonadotropins in girls was accompanied by a higher incidence of anxiety and depressive symptoms at the year's end. Relations between hormone levels and the adolescent's use of anger and power in parent-adolescent interactions indicated that boys with higher levels of androstenedione were higher on explosive behavior. Girls with higher levels of androstenedione were higher on dominance, defiance, and expression of anger toward both mother and father. Relations between hormone levels and degree of peripheral target tissue exposure and cognitive functioning indicated that boys with higher testosterone levels and a greater degree of peripheral target tissue exposure were higher on spatial abilities than boys with less exposure to circulating gonadal steroids. Neither hormone levels nor degree of peripheral target tissue exposure was related to spatial abilities in girls.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02164-06 LDP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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The Impact of Biological Changes on Psychological Functioning During Adolescence

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PI:	E.J. Susman	Guest Researcher	LDP NIMH
OTHER:	E.D. Nottelmann	Research Psychologist	LDP NIMH
	G.I. Germain	Research Psychologist	LDP NIMH
	L.D. Dorn	Guest Researcher	LDP NIMH
	G.P. Chrousos	Senior Investigator	DEB NICHD
	G.B. Cutler	Senior Investigator	DEB NICHD
	D.L. Loriaux	Chief	DEB NICHD

COOPERATING UNITS *(if any)*

Developmental Endocrinology, NICHD

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL ~~MAN-YEARS~~ Person Years	PROFESSIONAL:	OTHER:
2.92	1.07	1.85

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.)*

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02169-04 LDP

PERIOD COVERED
October 1, 1985 through September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Interactions Between Siblings with a Depressed Parent

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	C. Zahn-Waxler	Research Psychologist	LDP NIMH
OTHER:	D. Hay	Research Psychologist	Univ. of London
	M. Radke-Yarrow	Chief	LDP NIMH

COOPERATING UNITS *(if any)*
Univ. of London

LAB/BRANCH
Laboratory of Developmental Psychology

SECTION
Child Behavior Disorders

INSTITUTE AND LOCATION
National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL ~~MAN-YEARS~~ Persons Years	PROFESSIONAL:	OTHER:
.55	.20	.35

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.)*

Patterns of conflict and conflict resolution in the parent-child relationship undoubtedly impact on the relationships between siblings. The aim of this research is to examine the links between mother-child interactions and sibling interactions in the domains of conflict and interpersonal problem-solving. These patterns of behavior are examined in normal families and in families in which there is maternal depression. Siblings (2-3 years old and 5-7 years old) are observed in interaction with each other, individually with the mother, and together with the mother. Children's interpretations of conflict situations and understanding of others' emotions are also evaluated. High levels of conflict have been observed in some siblings with a depressed mother. Also interpretations of affect in projective tests suggest more disturbance and deviant themes in children with a depressed caregiver. Sex differences in patterns of conflict and negotiation of problems are of special interest because of their relevance to the differential development in the two sexes of antisocial and depressive disorders. Preliminary analyses indicate early sex differences in children's patterns of conflict resolution. Boys adopt more assertive and aggressive strategies for solving interpersonal problems while girls adopt more affiliative and submissive strategies for resolving conflicts.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02169-04 LDP

PERIOD COVERED
October 1, 1985 through September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
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PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	C. Zahn-Waxler	Research Psychologist	LDP NIMH
OTHER:	D. Hay	Research Psychologist	Univ. of London
	M. Radke-Yarrow	Chief	LDP NIMH

COOPERATING UNITS *(if any)*
Univ. of London

LAB/BRANCH
Laboratory of Developmental Psychology

SECTION
Child Behavior Disorders

INSTITUTE AND LOCATION
National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS: Persons Years	PROFESSIONAL:	OTHER:
.55	.20	.35

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.)*

Patterns of conflict and conflict resolution in the parent-child relationship undoubtedly impact on the relationships between siblings. The aim of this research is to examine the links between mother-child interactions and sibling interactions in the domains of conflict and interpersonal problem-solving. These patterns of behavior are examined in normal families and in families in which there is maternal depression. Siblings (2-3 years old and 5-7 years old) are observed in interaction with each other, individually with the mother, and together with the mother. Children's interpretations of conflict situations and understanding of others' emotions are also evaluated. High levels of conflict have been observed in some siblings with a depressed mother. Also interpretations of affect in projective tests suggest more disturbance and deviant themes in children with a depressed caregiver. Sex differences in patterns of conflict and negotiation of problems are of special interest because of their relevance to the differential development in the two sexes of antisocial and depressive disorders. Preliminary analyses indicate early sex differences in children's patterns of conflict resolution. Boys adopt more assertive and aggressive strategies for solving interpersonal problems while girls adopt more affiliative and submissive strategies for resolving conflicts.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02170-04 LDP

PERIOD COVERED
October 1, 1985 through September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Psychiatric Assessment of Infants and Toddlers

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	L. Cytryn	Medical Officer (Psychiatric)	LDP NIMH
Others:	T. Sherman	Senior Staff Fellow	LDP NIMH
	D. McKnew, Jr.	Medical Officer (Psychiatric)	LDP NIMH
	M. Radke-Yarrow	Chief	LDP NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH
Laboratory of Developmental Psychology

SECTION
Section on Affective Development

INSTITUTE AND LOCATION
National Institute of Mental Health, Bethesda, Maryland

TOTAL ~~MAN-YEARS~~ Person Years:	PROFESSIONAL:	OTHER:
2.20	1.10	1.10

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.)*

Ninety-four children, 2-3 years of age, were assessed using two structured, behavioral observation systems: in a psychiatric play interview in the absence of mother, (see Z01 MH 02170-03), and in interaction with mother (see Z01 MH 02230-02). Fifteen mothers had Bipolar Disorder, 37 Major Depressive Disorder, 9 Minor Depressive Disorder, and 33 with no history of psychiatric disorder. Approximately one-half of the husbands of the mothers with affective disorder had affective disorder as well.

All children were assigned a rating of degree of risk for the later development of psychopathology based on their performance in each of the two assessment settings. This pair of assessments produced four groups of children: a low risk group who received ratings of low risk for the later development of psychopathology in both assessments, two mixed-risk groups composed of children who received a rating of high risk in one setting, and low risk in the other, and a high risk group of children who received ratings of high risk in both assessments.

At this time, case by case analysis of the ten children in the high risk group is complete. Of these ten children, only 3 were girls. Two of the boys were from families in which neither parent had a history of psychiatric illness; of the remaining 8 children, 5 were from families in which both parents had affective disorder, and 3 from families with one ill parent.

Two major constellations of behavioral symptoms were discernible in these high-risk toddlers. One consisted of an isolated or distant type of relationship with mother, dysphoria, and anhedonia. The other consisted of an angry type of relationship with mother, and predominantly angry mood. The children in both groups demonstrated dysregulation of emotions under stress.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02170-04 LDP

PERIOD COVERED
October 1, 1985 through September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Psychiatric Assessment of Infants and Toddlers

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	L. Cytryn	Medical Officer (Psychiatric)	LDP NIMH
Others:	T. Sherman	Senior Staff Fellow	LDP NIMH
	D. McKnew, Jr.	Medical Officer (Psychiatric)	LDP NIMH
	M. Radke-Yarrow	Chief	LDP NIMH

COOPERATING UNITS *(if any)*
None

LAB/BRANCH
Laboratory of Developmental Psychology

SECTION
Section on Affective Development

INSTITUTE AND LOCATION
National Institute of Mental Health, Bethesda, Maryland

TOTAL MAN-YEARS: Person Years	PROFESSIONAL:	OTHER:
2.20	1.10	1.10

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.)*

Ninety-four children, 2-3 years of age, were assessed using two structured, behavioral observation systems: in a psychiatric play interview in the absence of mother, (see Z01 MH 02170-03), and in interaction with mother (see Z01 MH 02230-02). Fifteen mothers had Bipolar Disorder, 37 Major Depressive Disorder, 9 Minor Depressive Disorder, and 33 with no history of psychiatric disorder. Approximately one-half of the husbands of the mothers with affective disorder had affective disorder as well.

All children were assigned a rating of degree of risk for the later development of psychopathology based on their performance in each of the two assessment settings. This pair of assessments produced four groups of children: a low risk group who received ratings of low risk for the later development of psychopathology in both assessments, two mixed-risk groups composed of children who received a rating of high risk in one setting, and low risk in the other, and a high risk group of children who received ratings of high risk in both assessments.

At this time, case by case analysis of the ten children in the high risk group is complete. Of these ten children, only 3 were girls. Two of the boys were from families in which neither parent had a history of psychiatric illness; of the remaining 8 children, 5 were from families in which both parents had affective disorder, and 3 from families with one ill parent.

Two major constellations of behavioral symptoms were discernible in these high-risk toddlers. One consisted of an isolated or distant type of relationship with mother, dysphoria, and anhedonia. The other consisted of an angry type of relationship with mother, and predominantly angry mood. The children in both groups demonstrated dysregulation of emotions under stress.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02171-03 LDP

PERIOD COVERED
October 1, 1985 through September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Protective and Risk Factors in Childrearing: Contributions of Fathers

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	W.E. Wilson	Research Psychologist	DRG NIH
OTHER:	M.Radke-Yarrow	Chief	LDP NIMH

COOPERATING UNITS *(if any)*
Division of Research Grants
National Institutes of Health

LAB/BRANCH
Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION
National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MANYEARS: Person Years	PROFESSIONAL:	OTHER:
.45	.15	.50

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 research is focused on paternal contributions to child development. In particular, the role of fathers with wives with affective disorders is examined. Families are selected for the study on the basis of the mother's diagnoses, as normal or depressed. Fathers, mothers, and two children (ages 5-6 & 8-11) are observed in interaction in a home-like environment established in the laboratory. They participate in a variety of planned situations representative of day-to-day family events. The family members are observed in dyads and triads as well as a total group. The father is also interviewed: a psychiatric assessment (SADS) and an interview concerning his involvement in childrearing. Well fathers with well spouses describe fathering as involving regularly occurring contact with their children that is most often father-initiated, occurs at home, and involves intimate activities, e.g. reading stories or carrying on a conversation. On the other hand well fathers with ill spouses describe events that are "special," non-routine, are child-initiated, occur away from home, and involve physical play or outings. Analysis of interview and interaction data is continuing.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02171-03 LDP

PERIOD COVERED
October 1, 1985 through September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
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PI:	W.E. Wilson	Research Psychologist	DRG NIH
OTHER:	M.Radke-Yarrow	Chief	LDP NIMH

COOPERATING UNITS *(if any)*
Division of Research Grants
National Institutes of Health

LAB/BRANCH
Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION
National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS: Person Years	PROFESSIONAL:	OTHER:
.45	.15	.50

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 research is focused on paternal contributions to child development. In particular, the role of fathers with wives with affective disorders is examined. Families are selected for the study on the basis of the mother's diagnoses, as normal or depressed. Fathers, mothers, and two children (ages 5-6 & 8-11) are observed in interaction in a home-like environment established in the laboratory. They participate in a variety of planned situations representative of day-to-day family events. The family members are observed in dyads and triads as well as a total group. The father is also interviewed: a psychiatric assessment (SADS) and an interview concerning his involvement in childrearing. Well fathers with well spouses describe fathering as involving regularly occurring contact with their children that is most often father-initiated, occurs at home, and involves intimate activities, e.g. reading stories or carrying on a conversation. On the other hand well fathers with ill spouses describe events that are "special," non-routine, are child-initiated, occur away from home, and involve physical play or outings. Analysis of interview and interaction data is continuing.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02172-03 LDP

PERIOD COVERED
October 1, 1985 through September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Mothers as Mediators of Cognitive Development

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: S.L. Friedman	Guest Researcher	LDP NIMH
OTHER: M.A. Gordon	Research Psychologist	Div. of Prevention & Special Mental Health Programs, NIMH

COOPERATING UNITS *(if any)*
Division of Prevention and Special Mental Health Programs, NIMH

LAB/BRANCH
Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION
National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

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

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

Both investigators have taken other positions. Further work on the project will be carried on outside the Laboratory.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02172-03 LDP

PERIOD COVERED
October 1, 1985 through September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Mothers as Mediators of Cognitive Development

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: S.L. Friedman	Guest Researcher	LDP NIMH
OTHER: M.A. Gordon	Research Psychologist	Div. of Prevention & Special Mental Health Programs, NIMH

COOPERATING UNITS *(if any)*
Division of Prevention and Special Mental Health Programs, NIMH

LAB/BRANCH
Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION
National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

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

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

Both investigators have taken other positions. Further work on the project will be carried on outside the Laboratory.

GPO 914-916

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02173-03 LDP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Sex Identity Development in Young Offspring of Well and Depressed Mothers

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	T.L. Sherman	Senior Staff Fellow	LDP NIMH
OTHER:	G. Kochanska	Senior Staff Fellow	LDP NIMH
	M. Radke-Yarrow	Chief	LDP NIMH

COOPERATING UNITS *(if any)*

NONE

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

CHECK APPROPRIATE BOX(ES)

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

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

This project has been incorporated into project Z01 MH 02207.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02173-03 LDP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Sex Identity Development in Young Offspring of Well and Depressed Mothers

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	T.L. Sherman	Senior Staff Fellow	LDP NIMH
OTHER:	G. Kochanska	Senior Staff Fellow	LDP NIMH
	M. Radke-Yarrow	Chief	LDP NIMH

COOPERATING UNITS *(if any)*

NONE

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

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 incorporated into project Z01 MH 02207.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02174-03 LDP

PERIOD COVERED
October 1, 1985 through September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Parental Beliefs Regarding the Origins of Their Children's Behavior

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	G. Kochanska	Senior Staff Fellow	LDP NIMH
OTHER:	M. Radke-Yarrow	Chief	LDP NIMH
	L.J. Kuczynski	Assoc. Professor	Univ. of Guelph, Ontario, Canada
	S.L. Friedman	Guest Researcher	LDP NIMH

COOPERATING UNITS *(if any)*
University of Guelph, Ontario, Canada

LAB/BRANCH
Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION
National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL ~~MAN-YEARS~~ Person Years:	PROFESSIONAL:	OTHER:
.62	.32	.30

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 structure of mothers' beliefs regarding the development of their children is investigated in families with and without parental depression. Depressive cognitive schemas, such as self-derogation and lack of perceived control over events, are examined in relation to depressed mothers' perception of their children's development. How mothers perceive their own causal role as a caregiver compared to other causal agents (genetics, father's input, uncontrollable factors), and how satisfied they are with their children's development may be a crucial influence on mothers' rearing practices and expectations conveyed to their children. Seventy-seven well, unipolar and bipolar depressed mothers' beliefs about their children's affective, cognitive and social development were assessed by means of a questionnaire and interview. Unipolar depressed mothers, more so than other groups, were concerned with their children's affective and social development as compared to cognitive development. The affectively ill women, particularly bipolar depressed, felt more helpless regarding their children's development than well women.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02174-03 LDP

PERIOD COVERED
October 1, 1985 through September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
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PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	G. Kochanska	Senior Staff Fellow	LDP NIMH
OTHER:	M. Radke-Yarrow	Chief	LDP NIMH
	L.J. Kuczynski	Assoc. Professor	Univ. of Guelph, Ontario, Canada
	S.L. Friedman	Guest Researcher	LDP NIMH

COOPERATING UNITS *(if any)*
University of Guelph, Ontario, Canada

LAB/BRANCH
Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION
National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL ~~MAN-YEARS~~ Person Years:	PROFESSIONAL:	OTHER:
.62	.32	.30

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 structure of mothers' beliefs regarding the development of their children is investigated in families with and without parental depression. Depressive cognitive schemas, such as self-derogation and lack of perceived control over events, are examined in relation to depressed mothers' perception of their children's development. How mothers perceive their own causal role as a caregiver compared to other causal agents (genetics, father's input, uncontrollable factors), and how satisfied they are with their children's development may be a crucial influence on mothers' rearing practices and expectations conveyed to their children. Seventy-seven well, unipolar and bipolar depressed mothers' beliefs about their children's affective, cognitive and social development were assessed by means of a questionnaire and interview. Unipolar depressed mothers, more so than other groups, were concerned with their children's affective and social development as compared to cognitive development. The affectively ill women, particularly bipolar depressed, felt more helpless regarding their children's development than well women.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02175-03 LDP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Natural Discourse of Normal and Depressed Mothers and Their Young Children

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	M. Radke-Yarrow	Chief	LDP NIMH
OTHER:	B. Belmont	Social Science Analyst	LDP NIMH
	A. Mayfield	Psychology Technician	LDP NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS: ~~xxxxxx~~Person Years	PROFESSIONAL:	OTHER:
1.35	.20	1.15

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.)*

The early development of children's self-conceptions is believed to be heavily determined within the family. The mother's comments to and about her child are one plausible contributor to the child's self-knowledge and self-regard. To ascertain the nature of this influence, the natural discourse of mothers and their young children was investigated. The verbalizations of depressed mothers are of special interest because of problems of self-concept and self-esteem characteristic of depression. Thirty-five minutes of mother and child speech were sampled from naturalistic interactions (See Z01 MH 02144). Transcriptions of verbalizations were made from audio-videotaped records. The content of the verbalizations of 17 well and 18 depressed mothers and their 2- to 3-year-old children was examined. Mother's utterances and child utterances were independently coded.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02175-03 LDP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

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PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	M. Radke-Yarrow	Chief	LDP NIMH
OTHER:	B. Belmont	Social Science Analyst	LDP NIMH
	A. Mayfield	Psychology Technician	LDP NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS: XXXXXXPerson Years	PROFESSIONAL:	OTHER:
1.35	.20	1.15

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.)*

The early development of children's self-conceptions is believed to be heavily determined within the family. The mother's comments to and about her child are one plausible contributor to the child's self-knowledge and self-regard. To ascertain the nature of this influence, the natural discourse of mothers and their young children was investigated. The verbalizations of depressed mothers are of special interest because of problems of self-concept and self-esteem characteristic of depression. Thirty-five minutes of mother and child speech were sampled from naturalistic interactions (See Z01 MH 02144). Transcriptions of verbalizations were made from audio-videotaped records. The content of the verbalizations of 17 well and 18 depressed mothers and their 2- to 3-year-old children was examined. Mother's utterances and child utterances were independently coded.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02207-03 LDP

PERIOD COVERED
October 1, 1985 through September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
The Affective Rearing Environment: A Comparison of Normal and Depressed Parents

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	M. Radke-Yarrow	Chief	LDP NIMH
OTHER:	G. Kochanska	Senior Staff Fellow	LDP NIMH
	L. Kuczynski	Assoc. Professor	Univ. of Guelph
	E. Nottelmann	Research Psychologist	LDP NIMH
	W.E. Wilson, Jr.	Research Psychologist	DRG NIH
	B. Belmont	Social Science Analyst	LDP NIMH
	A. Mayfield	Psychology Technician	LDP NIMH
	A. Polissar	Psychologist	LDP NIMH
	J. Stilwell	Res. Nurse Prac. (Psychiatric)	LDP NIMH

COOPERATING UNITS *(if any)*
Division of Research Grants, NIH
Univ. of Guelph, Guelph, Ontario, Canada

LAB/BRANCH
Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION
National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL ~~MAN-YEARS~~ PERSON YEARS:	PROFESSIONAL:	OTHER:
5.44	.79	4.65

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.)*

Affective dimensions of normal and depressed mothers' and children's behavior are investigated. It was hypothesized that children's experiences in the family environment provided by depressed parents would diverge significantly from normal families. Based on continuous coding of the moods and emotions of mothers and children over 9 hours of interaction, the following significant group differences were found: Significantly more time was rated as negative in mood or in specific negative emotions, (sad, fearful, angry, or anxious) for depressed mothers and their 2- to 3-year-olds and 5-to-7-year-olds than for normal mother-child dyads. The quality rather than the frequency of affection differs in the normal and depressed groups. There is very high co-occurrence (matches by minute) of affective expression by mother and young child, particularly for depressed mothers and their daughters. Analyses are underway on three related aspects of the socialization and regulation of affect.
In all of the studies, the source of data is project (Z01-MH-02144), involving observation of mothers' and children's moods and emotions in relation to a variety of situations.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02207-03 LDP

PERIOD COVERED
October 1, 1985 through September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
The Affective Rearing Environment: A Comparison of Normal and Depressed Parents

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	M. Radke-Yarrow	Chief	LDP NIMH
OTHER:	G. Kochanska	Senior Staff Fellow	LDP NIMH
	L. Kuczynski	Assoc. Professor	Univ. of Guelph
	E. Nottelmann	Research Psychologist	LDP NIMH
	W.E. Wilson, Jr.	Research Psychologist	DRG NIH
	B. Belmont	Social Science Analyst	LDP NIMH
	A. Mayfield	Psychology Technician	LDP NIMH
	A. Polissar	Psychologist	LDP NIMH
	J. Stilwell	Res. Nurse Prac. (Psychiatric)	LDP NIMH

COOPERATING UNITS *(if any)*
Division of Research Grants, NIH
Univ. of Guelph, Guelph, Ontario, Canada

LAB/BRANCH
Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION
National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS: PERSON YEARS	PROFESSIONAL:	OTHER:
5.44	.79	4.65

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.)*

Affective dimensions of normal and depressed mothers' and children's behavior are investigated. It was hypothesized that children's experiences in the family environment provided by depressed parents would diverge significantly from normal families. Based on continuous coding of the moods and emotions of mothers and children over 9 hours of interaction, the following significant group differences were found: Significantly more time was rated as negative in mood or in specific negative emotions, (sad, fearful, angry, or anxious) for depressed mothers and their 2- to 3-year-olds and 5-to-7-year-olds than for normal mother-child dyads. The quality rather than the frequency of affection differs in the normal and depressed groups. There is very high co-occurrence (matches by minute) of affective expression by mother and young child, particularly for depressed mothers and their daughters. Analyses are underway on three related aspects of the socialization and regulation of affect.
In all of the studies, the source of data is project (Z01-MH-02144), involving observation of mothers' and children's moods and emotions in relation to a variety of situations.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02210-03 LDP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Symbolic Functioning in Play of Depressed and Well Mothers and Their Children

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	K.C. Barrett	Research Psychologist	Univ. of Wyoming
OTHER:	S.L. Friedman	Guest Researcher	LDP NIMH
	D. Wolf	Research Psychologist	Harvard Univ.
	M. Watson	Associate Professor	Brandeis Univ.

COOPERATING UNITS *(if any)*

Harvard University
Brandeis University
Univ. of Wyoming

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS: ~~Person Years~~	PROFESSIONAL:	OTHER:

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.)*

Investigators have taken other positions. Further work on the project will be carried on outside the Laboratory.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02210-03 LDP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Symbolic Functioning in Play of Depressed and Well Mothers and Their Children

PRINCIPAL INVESTIGATOR *(List other prolessional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	K.C. Barrett	Research Psychologist	Univ. of Wyoming
OTHER:	S.L. Friedman	Guest Researcher	LDP NIMH
	D. Wolf	Research Psychologist	Harvard Univ.
	M. Watson	Associate Professor	Brandeis Univ.

COOPERATING UNITS *(il any)*

Harvard University
Brandeis University
Univ. of Wyoming

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS: XXXXXX Person Years	PROFESSIONAL:	OTHER:

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.)*

Investigators have taken other positions. Further work on the project will be carried on outside the Laboratory.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02229-02 LDP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Vocalic Analysis of Natural Discourse in Well and Depressed Mothers

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	T.L. Sherman	Senior Staff Fellow	LDP NIMH
OTHER:	Z. Breznitz	Research Psychologist	University of Haifa
	M. Radke-Yarrow	Chief	LDP NIMH

COOPERATING UNITS *(if any)*

University of Haifa, Israel

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL ~~MAN-YEARS~~ Person Years	PROFESSIONAL:	OTHER:
1.15	.40	.75

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 speech behavior of 14 depressed and 18 nondepressed mothers during conversation with their 3-year-old children was examined in this study. Given the general motor retardation, the reduced energy level and the social withdrawal of depressed individuals, the speech patterns of depressed mothers were predicted to differ from the speech patterns of well mothers. The results were consistent with the preliminary findings reported in last year's Annual Report Z01 MH 02229-01 LDP. Depressed mothers vocalized less often and responded less quickly to the cessation of their children's speech than healthy mothers. However, in a mildly stressful situation, (awaiting a doctor's visit), the depressed mothers, but not the healthy mothers, significantly increased their level of speech productivity. Children of the depressed mothers spoke less than children of healthy women, particularly while sitting and eating lunch with their mothers. The observed differences in the mothers' behaviors were interpreted as an indication that the two groups of children are exposed to very different patterns of socialization. The offspring of depressed women are being taught both to keep social interaction to a minimum and to be overreactive to even mild stresses. The differences in the children's behavior may indicate that already these 3-year-old children have learned to keep their interactions with their mother to a minimum. This manner of adaptation may have negative effects on the child's continued social, emotional and cognitive development.

Preliminary analyses are available from the second study which focused on voice characteristics of the mother in an interview in which she was questioned concerning the dominant mood state of her child, her husband and herself. Overall the depressed mothers reported less positive mood states for all family members than did the normal women. However, even when restricting the assessed speech sample to statements with a positive or neutral content, the range of the voice's frequency was restricted for the depressed women.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02229-02 LDP

PERIOD COVERED
October 1, 1985 through September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Vocalic Analysis of Natural Discourse in Well and Depressed Mothers

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	T.L. Sherman	Senior Staff Fellow	LDP NIMH
OTHER:	Z. Breznitz	Research Psychologist	University of Haifa
	M. Radke-Yarrow	Chief	LDP NIMH

COOPERATING UNITS *(if any)*
University of Haifa, Israel

LAB/BRANCH
Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION
National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS: Person Years	PROFESSIONAL:	OTHER:
1.15	.40	.75

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 speech behavior of 14 depressed and 18 nondepressed mothers during conversation with their 3-year-old children was examined in this study. Given the general motor retardation, the reduced energy level and the social withdrawal of depressed individuals, the speech patterns of depressed mothers were predicted to differ from the speech patterns of well mothers. The results were consistent with the preliminary findings reported in last year's Annual Report Z01 MH 02229-01 LDP. Depressed mothers vocalized less often and responded less quickly to the cessation of their children's speech than healthy mothers. However, in a mildly stressful situation, (awaiting a doctor's visit), the depressed mothers, but not the healthy mothers, significantly increased their level of speech productivity. Children of the depressed mothers spoke less than children of healthy women, particularly while sitting and eating lunch with their mothers. The observed differences in the mothers' behaviors were interpreted as an indication that the two groups of children are exposed to very different patterns of socialization. The offspring of depressed women are being taught both to keep social interaction to a minimum and to be overreactive to even mild stresses. The differences in the children's behavior may indicate that already these 3-year-old children have learned to keep their interactions with their mother to a minimum. This manner of adaptation may have negative effects on the child's continued social, emotional and cognitive development.

Preliminary analyses are available from the second study which focused on voice characteristics of the mother in an interview in which she was questioned concerning the dominant mood state of her child, her husband and herself. Overall the depressed mothers reported less positive mood states for all family members than did the normal women. However, even when restricting the assessed speech sample to statements with a positive or neutral content, the range of the voice's frequency was restricted for the depressed women.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02230-02 LDP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Psychiatric Assessment of 5-10 Year Old Children at Risk for Affective Disorder

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D. McKnew, Jr.	Medical Officer (Psychiatry)	LDP NIMH
Others:	T. Sherman	Senior Staff Fellow	LDP NIMH
	L. Cytryn	Medical Officer (Psychiatry)	LDP NIMH
	M. Radke-Yarrow	Chief	LDP NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

Section on Affective Development

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland

TOTAL MAN-YEARS: Person Years	PROFESSIONAL:	OTHER:
1.85	.85	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 project concerns the offspring data and follow-up data derived from psychiatric interviews of the five to ten year old children of the families in the NIMH Childrearing Project (Z01 MH 02144). At time of recruitment one child was between five and eight years of age, and one child was between two and three years of age. At initial assessment, the older child was administered the CAS (Child Assessment Schedule), and diagnosed according to the DSM-III criteria. Three years later, the younger children, now 5 - 8 years of age, and the older children, now 7-10 years of age, were both assessed with the CAS instrument and both groups of children were diagnosed using the DSM-III criteria. Thus, this project provides data concerning child psychiatric status as a function of parental psychopathology, as well as data concerning short term consistency of psychiatric status in children of these ages.

More of the children whose mothers had affective disorder received DSM-III diagnoses. This trend reached significance for the younger children at the second time of assessment, but did not reach significance for the older children. Also more of the children whose parents have major affective disorder received diagnoses at both times of assessment, than did the children whose parents have no history of psychiatric disorder.

Longitudinal assessment of the children of affectively ill and healthy parents will enable us to identify ages at which the appearance of affective disturbance is common, but not predictive of continued psychopathology, and hopefully, points in development when the appearance of affective disturbance is predictive of continued psychopathology.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02230-02 LDP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

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PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D. McKnew, Jr.	Medical Officer (Psychiatry)	LDP NIMH
Others:	T. Sherman	Senior Staff Fellow	LDP NIMH
	L. Cytryn	Medical Officer (Psychiatry)	LDP NIMH
	M. Radke-Yarrow	Chief	LDP NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

Section on Affective Development

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland

TOTAL MANYEARS: Person Years	PROFESSIONAL:	OTHER:
1.85	.85	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 project concerns the offspring data and follow-up data derived from psychiatric interviews of the five to ten year old children of the families in the NIMH Childrearing Project (Z01 MH 02144). At time of recruitment one child was between five and eight years of age, and one child was between two and three years of age. At initial assessment, the older child was administered the CAS (Child Assessment Schedule), and diagnosed according to the DSM-III criteria. Three years later, the younger children, now 5 - 8 years of age, and the older children, now 7-10 years of age, were both assessed with the CAS instrument and both groups of children were diagnosed using the DSM-III criteria. Thus, this project provides data concerning child psychiatric status as a function of parental psychopathology, as well as data concerning short term consistency of psychiatric status in children of these ages.

More of the children whose mothers had affective disorder received DSM-III diagnoses. This trend reached significance for the younger children at the second time of assessment, but did not reach significance for the older children. Also more of the children whose parents have major affective disorder received diagnoses at both times of assessment, than did the children whose parents have no history of psychiatric disorder.

Longitudinal assessment of the children of affectively ill and healthy parents will enable us to identify ages at which the appearance of affective disturbance is common, but not predictive of continued psychopathology, and hopefully, points in development when the appearance of affective disturbance is predictive of continued psychopathology.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02231-02 LDP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Biological-Behavioral Relations in Early Adolescence

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	E.D. Nottelmann	Research Psychologist	LDP NIMH
OTHER:	E.J. Susman	Guest Researcher	LDP NIMH
	G.I. Germain	Research Psychologist	LDP NIMH
	L.D. Dorn	Guest Researcher	LDP NIMH
	J. Welsh	Research Psychologist	LDP NIMH
	G.P. Chrousos	Senior Investigator	DEB NICHD
	G.B. Cutler, Jr.	Senior Investigator	DEB NICHD
	D.L. Loriaux	Chief	DEB NICHD

COOPERATING UNITS *(if any)*

Developmental Endocrinology, NICHD

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL ~~MAN-YEARS~~ Person Years	PROFESSIONAL:	OTHER:
.97	.57	.40

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.)*

Interrelations of markers of pubertal development (endocrine status, pubertal stage, and physical growth) and adolescent adjustment are investigated cross-sectionally and longitudinally. Participants are 9- to 14-year-old boys and girls and their parents. The adolescents and their parents are seen three times, six months apart. The markers of pubertal development include serum hormone levels (gonadotropins, sex steroids, and adrenal androgens), pubertal stage (Tanner criteria), and height and weight. Psychological assessments of the adolescent include measures of behavior problems, self-image regarding various domains of functioning, and self- and parent-perceptions of the adolescent's physical, cognitive, social, and overall competence. Cross-sectional hormone data for Time 2 and 3 were analyzed for the comparison with interrelations based on Time 1 data. In general, findings were replicated. Biological changes across Times 1-3 were examined to determine the rate and trajectory of biological change during the one-year period of the study. These analyses inform our tests for linear and nonlinear effects of biological processes on psychological functioning. Ongoing analyses of predictive relations between Time 1 biological measures and Time 3 psychological measures confirm some important findings from cross-sectional analyses. For example, higher levels of androstenedione and lower dehydroepiandrosterone sulphate levels continue to be associated with behavior problems. Timing of maturation as well as rate of biological change (in physical maturity for boys and hormone levels for girls) also predicted psychological functioning at Time 3. Analyses are planned to generate hormone profiles, so that individual hormone profiles may be examined in relation to competencies and dysfunctions in psychological domains.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02231-02 LDP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

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PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	E.D. Nottelmann	Research Psychologist	LDP NIMH
OTHER:	E.J. Susman	Guest Researcher	LDP NIMH
	G.I. Germain	Research Psychologist	LDP NIMH
	L.D. Dorn	Guest Researcher	LDP NIMH
	J. Welsh	Research Psychologist	LDP NIMH
	G.P. Chrousos	Senior Investigator	DEB NICHD
	G.B. Cutler, Jr.	Senior Investigator	DEB NICHD
	D.L. Loriaux	Chief	DEB NICHD

COOPERATING UNITS *(if any)*

Developmental Endocrinology, NICHD

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS: Person Years	PROFESSIONAL:	OTHER:
.97	.57	.40

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.)*

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02232-02 LDP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Development of Ability to Concentrate in Children of Depressed and Well Mothers

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Z. Breznitz	Research Psychologist	Univ. of Haifa Haifa, Israel
OTHER:	S.L. Friedman	Guest Researcher	LDP NIMH

COOPERATING UNITS *(if any)*

University of Haifa
Haifa, Israel

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN~~YEARS~~ Person Years	PROFESSIONAL:	OTHER:
.30	.10	.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.)*

Twenty-five mother-toddler dyads with depressed mothers were compared with 25 dyads with well mothers on measures of attention during 20 minutes of spontaneous play in a home-like setting. The children of the depressed women focused their attention on significantly more objects for significantly shorter durations of time. Depressed women initiated and terminated significantly more instances of attention to objects than did the well mothers. The correlations between the maternal behaviors and the children's attention behaviors were statistically significant. The results support the hypothesis that the poorer attention of children of depressed women as reported in the literature, is at least in part mediated by inculcation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02232-02 LDP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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PI:	Z. Breznitz	Research Psychologist	Univ. of Haifa Haifa, Israel
OTHER:	S.L. Friedman	Guest Researcher	LDP NIMH

COOPERATING UNITS *(if any)*

University of Haifa
Haifa, Israel

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS: Person Years	PROFESSIONAL:	OTHER:
.30	.10	.20

CHECK APPROPRIATE BOX(ES)

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

☒ (a1) Minors

☒ (a2) Interviews

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02233-01 LDP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

The Patterns of Communication about Emotions in Mother-Child Dyads

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	C. Zahn-Waxler	Research Psychologist	LDP NIMH
Others:	K. Barrett	Psychologist	University of Wyoming
	D. Ridgeway	Psychologist	Colorado State University
	I. Bretherton	Psychologist	Colorado State University
	S. Denham	Guest Researcher	LDP NIMH

COOPERATING UNITS *(if any)*

University of Wyoming
Colorado State University

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

Secion on Child Behavior Disorders

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland

TOTAL MAN-YEARS: ~~XX YEARS~~ Person Years	PROFESSIONAL:	OTHER:
.70	.20	.50

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 research focuses on the development of experimental procedures to assess mothers' styles of communication about emotions with their young children. Associations between mothers' and children's responses concerning emotions are explored. How interpretations of emotions are related to expressed behaviors are examined. Factors contributing to children's understanding of causes and consequences of psychological (emotion) events are examined, especially as they pertain to the early development of a sense of responsibility and guilt reactions. Preliminary analyses indicate that quantitative and qualitative variations in communication patterns are evident, both in the mothers and their two-year-olds. Subsequent analyses of emotion language in mother-child dyads will compare children of anxious or depressed mothers and of mothers without mood disturbance. Mothers' and children's discussions of causes of (negative) emotions also will be examined in relation to experimental assessments of children's feelings of responsibility and guilt reactions.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02233-01 LDP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

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Others:	K. Barrett	Psychologist	University of Wyoming
	D. Ridgeway	Psychologist	Colorado State University
	I. Bretherton	Psychologist	Colorado State University
	S. Denham	Guest Researcher	LDP NIMH

COOPERATING UNITS *(if any)*

University of Wyoming
Colorado State University

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

Secion on Child Behavior Disorders

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland

TOTAL MAN-YEARS: ~~Person Years~~	PROFESSIONAL:	OTHER:
.70	.20	.50

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.)*

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02234-01 LDP

PERIOD COVERED

October 1, 1985 through September30, 1986

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

Infants of Chronically Depressed, Bipolar, and Normal Parents

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	K. Suter	Medical Staff Fellow	LDP NIMH
OTHER:	J. Stilwell	Research Nurse Practitioner (Psychiatric)	LDP NIMH

COOPERATING UNITS *(if any)*

NONE

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

Section on Affective Development

INSTITUTE AND LOCATION

National Institute of Mental Health

TOTAL MANXYEARS: Person Years	PROFESSIONAL:	OTHER:
1.41	1.00	.41

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.)*

Research has shown that children of depressed parents are at risk for development of affective illness, but little is known about the effects of parental affective psychopathology on infants during the first eighteen months of life. This study examines early affective regulation, attachment behavior, and patterns of mother-infant interaction in infants of four groups of parents: (1) bipolar mothers and well fathers, (2) bipolar fathers and well mothers, (3) chronically depressed mothers and well fathers, and (4) both parents without psychiatric illness. Infants and their mothers are observed and videotaped in a set of standardized situations in a homelike laboratory setting on two occasions five months apart, beginning when the infants are aged 3 months, 8 months, or 13 months. Data collection has begun recently and findings are not yet available. Analyses are planned to examine both individual and group differences in an attempt to look for possible precursors to later difficulties in this at-risk population.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02234-01 LDP

PERIOD COVERED

October 1, 1985 through September30, 1986

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PI:	K. Suter	Medical Staff Fellow	LDP NIMH
OTHER:	J. Stilwell	Research Nurse Practitioner (Psychiatric)	LDP NIMH

COOPERATING UNITS *(if any)*

NONE

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

Section on Affective Development

INSTITUTE AND LOCATION

National Institute of Mental Health

TOTAL MANYEARS: Person Years	PROFESSIONAL:	OTHER:
1.41	1.00	.41

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.)*

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02297-01 LDP

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Generosity and sharing in children of normal or affectively disturbed parents

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	F.R. Ascione	Guest Researcher	LDP NIMH
OTHERS:	M. Radke-Yarrow	Chief	LDP NIMH
	C. Zahn-Waxler	Research Psychologist	LDP NIMH

COOPERATING UNITS *(if any)*

Section on Child Behavior Disorders

LAB/BRANCH

Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION

National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS: ~~XXXXX~~ Person Years	PROFESSIONAL:	OTHER:
.55	.25	.30

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 ability to relate positively to other persons is an important aspect of development. One indicator of this achievement is the child's capacity for empathy and ability to help or share with another person. The purposes of this study are to: (1) examine 5-9 year old children's generosity in a laboratory measure of sharing and also in a naturalistic setting with their younger siblings; and (2) explore proximal and distal correlates of generosity and sharing, and their relation to parental diagnostic status (affectively disturbed or normal). (3) There is also a methodological interest in comparing the standard laboratory measure of sharing that has been the basis of the majority of studies of sharing with measures of sharing in the context of the child's family interactions. This study uses data collected during the first phase of a longitudinal study of child rearing and parental affective disorders.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02297-01 LDP

PERIOD COVERED
October 1, 1985 through September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Generosity and sharing in children of normal or affectively disturbed parents

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	F.R. Ascione	Guest Researcher	LDP NIMH
OTHERS:	M. Radke-Yarrow	Chief	LDP NIMH
	C. Zahn-Waxler	Research Psychologist	LDP NIMH

COOPERATING UNITS *(if any)*
Section on Child Behavior Disorders

LAB/BRANCH
Laboratory of Developmental Psychology

SECTION

INSTITUTE AND LOCATION
National Institute of Mental Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS: ~~XXXXXX~~ Person Years	PROFESSIONAL:	OTHER:
.55	.25	.30

CHECK APPROPRIATE BOX(ES)
- ☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
  - ☒ (a1) Minors
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SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the space provided.)*

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00450-12 CP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Biological Rhythms in Illness

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D.A. Sack	Chief, Inpatient Services	CPB/NIMH
Others:	W.B. Mendelson	Chief, Unit on Sleep Studies	CPB/NIMH
	W.C. Duncan	Research Psychologist	CPB/NIMH
	N.E. Rosenthal	Chief, Outpatient Services	CPB/NIMH
	R. Skwerer	Clinical Associate	CPB/NIMH
	F.M. Jacobsen	Clinical Associate	CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	.5	.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 timing of circadian oscillators cannot be measured directly in humans and indirect measures such as the secretory profiles of hormones, body temperature and EEG sleep recordings must suffice instead. External and internal factors called masking can influence the apperent circadian rhythms in these variables without affecting the biological clock or clocks. In our present study, we have been comparing the circadian system of depressed patients and normal controls under routine ward conditions and then repeating these measurements in conditions where the internal and external sources of masking have been controlled by holding diet, activity, posture, lighting and wakefulness constant.

Preliminary data of the temperature rhythm in patients with affective disorders confirm that mean body temperature is increased in both depression and mania compared to controls and the timing, or phase of the temperature is shifted to an abnormally early time in both phases of the illness. The disturbances in temperature cannot be attributed to masking since they persist under constant conditions. Consistent with our previous observations made in a group of rapid-cycling manic depressives, patients with major depression show a decreased nocturnal rise in TSH and diminished TSH response to sleep deprivation. The disturbance in temperature regulation in association with abnormal hypothalamic-pituitary-thyroid function may be indicative of an underlying disorder of metabolism in patients with major depression.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 00450-12 CP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Biological Rhythms in Illness

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D.A. Sack	Chief, Inpatient Services	CPB/NIMH
Others:	W.B. Mendelson	Chief, Unit on Sleep Studies	CPB/NIMH
	W.C. Duncan	Research Psychologist	CPB/NIMH
	N.E. Rosenthal	Chief, Outpatient Services	CPB/NIMH
	R. Skwerer	Clinical Associate	CPB/NIMH
	F.M. Jacobsen	Clinical Associate	CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	.5	.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 timing of circadian oscillators cannot be measured directly in humans and indirect measures such as the secretory profiles of hormones, body temperature and EEG sleep recordings must suffice instead. External and internal factors called masking can influence the apperent circadian rhythms in these variables without affecting the biological clock or clocks. In our present study, we have been comparing the circadian system of depressed patients and normal controls under routine ward conditions and then repeating these measurements in conditions where the internal and external sources of masking have been controlled by holding diet, activity, posture, lighting and wakefulness constant.

Preliminary data of the temperature rhythm in patients with affective disorders confirm that mean body temperature is increased in both depression and mania compared to controls and the timing, or phase of the temperature is shifted to an abnormally early time in both phases of the illness. The disturbances in temperature cannot be attributed to masking since they persist under constant conditions. Consistent with our previous observations made in a group of rapid-cycling manic depressives, patients with major depression show a decreased nocturnal rise in TSH and diminished TSH response to sleep deprivation. The disturbance in temperature regulation in association with abnormal hypothalamic-pituitary-thyroid function may be indicative of an underlying disorder of metabolism in patients with major depression.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02193-04 CP

PERIOD COVERED
October 1, 1985 to September 30, 1986

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

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
PI: W. B. Mendelson Chief, Section on Sleep Studies CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Psychobiology Branch

SECTION
Section on Sleep Studies

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

Our work has suggested that insomniacs may have cognitive disorders by day, manifested by a decrease in semantic memory (the ability to retrieve or use material already well learned) and also suggested that cognitive processes during sleep may also be altered. The current study has pursued this possibility, by testing arousal thresholds to meaningless and meaningful stimuli during sleep, ability to respond to commands during sleep, and similar measures. We have found that although arousal thresholds differed significantly between sleep stages, there were no differences between insomniacs and normals. Insomniacs returned to sleep and stayed asleep between arousal tests with the same facility as controls, but believed that they had slept only half as long. There is further evidence, then, that insomniacs suffer from misperception of their state of consciousness.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02193-04 CP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Clinical Studies of Insomnia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: W. B. Mendelson Chief, Section on Sleep Studies CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

Section on Sleep Studies

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

Our work has suggested that insomniacs may have cognitive disorders by day, manifested by a decrease in semantic memory (the ability to retrieve or use material already well learned) and also suggested that cognitive processes during sleep may also be altered. The current study has pursued this possibility, by testing arousal thresholds to meaningless and meaningful stimuli during sleep, ability to respond to commands during sleep, and similar measures. We have found that although arousal thresholds differed significantly between sleep stages, there were no differences between insomniacs and normals. Insomniacs returned to sleep and stayed asleep between arousal tests with the same facility as controls, but believed that they had slept only half as long. There is further evidence, then, that insomniacs suffer from misperception of their state of consciousness.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02200-04 CP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Light suppression of Nocturnal Human Melatonin Secretion

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	T. A. Wehr	Chief, Clinical Psychobiology Branch	CPB/NIMH
Others:	D. A. Sack	Chief, Inpatient Services	CPB/NIMH
	N. E. Rosenthal	Chief, Outpatient Services	CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	1.0	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.)*

Since our previous report we have been unable to consistently suppress melatonin secretion in normal controls using a ganzfeld dome to administer light of intensities up to 2500 lux. The basis for the difference in the physiological response to light administered via the dome and other light sources is not clear. Since our purpose in these experiments was to develop an improved methodology for assessing patient-normal differences in the sensitivity of melatonin secretion to suppression by light, the ganzfeld dome does not appear to be of value in this regard. We are therefore cancelling this project at this time.

GPO 914-916

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02200-04 CP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Light suppression of Nocturnal Human Melatonin Secretion

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	T. A. Wehr	Chief, Clinical Psychobiology Branch	CPB/NIMH
Others:	D. A. Sack	Chief, Inpatient Services	CPB/NIMH
	N. E. Rosenthal	Chief, Outpatient Services	CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	1.0	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.)*

Since our previous report we have been unable to consistently suppress melatonin secretion in normal controls using a ganzfeld dome to administer light of intensities up to 2500 lux. The basis for the difference in the physiological response to light administered via the dome and other light sources is not clear. Since our purpose in these experiments was to develop an improved methodology for assessing patient-normal differences in the sensitivity of melatonin secretion to suppression by light, the ganzfeld dome does not appear to be of value in this regard. We are therefore cancelling this project at this time.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02201-04 CP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Early Versus Late Partial Sleep Deprivation in the Treatment of Depression

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D. Sack	Chief, Inpatient Services	CPB/NIMH
Others:	T.A. Wehr	Chief, Clinical Psychobiology Branch	CPB/NIMH
	N.E. Rosenthal	Chief, Outpatient Services	CPB/NIMH
	B.L. Parry	Chinical Associate	CPB/NIMH
	W.B. Mendelson	Chief, Unit on Sleep Studies	CPB/NIMH
	S.P. James	Clinical Associate	CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

In our previous study of partial sleep deprivation (PSD), we considered both the timing of sleep and the duration of sleep as potential factors in determining response to treatment (annual report Z01 MH 0221-02 CP). We found that the clinical response to sleep deprivation was proportional to the reduction in sleep, and in particular REM sleep. The timing of sleep also appeared to be a factor with patients showing significantly greater improvement when sleep deprived in the second half of the night (PSD-L) than in the first half of the night (PSD-E). The effect of timing on the PSD response was confounded by the fact that patients sleep significantly less on the PSD-L condition. An additional finding of this study was that the antidepressant response to a single night of PSD could be extended by repeating the procedure for a second night.

In our present study, we are comparing the relative effects of PSD-L and PSD-E with the duration of sleep rigidly controlled. In a second study, we are assessing the cumulative antidepressant efficacy of PSD performed over a three week period. Six subjects have been studies to date. Our data is not sufficient to determine the relative efficacy of the two treatments but we have succeeded in achieving comparable sleep reductions on the two treatments. In the longitudinal study of PSD, two patients improved, one with complete remission of her depression, and four showing essentially no change with treatment. A larger sample will be required to establish whether PSD has sustained antidepressant effects in depression.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02201-04 CP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Early Versus Late Partial Sleep Deprivation in the Treatment of Depression

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D. Sack	Chief, Inpatient Services	CPB/NIMH
Others:	T.A. Wehr	Chief, Clinical Psychobiology Branch	CPB/NIMH
	N.E. Rosenthal	Chief, Outpatient Services	CPB/NIMH
	B.L. Parry	Chinical Associate	CPB/NIMH
	W.B. Mendelson	Chief, Unit on Sleep Studies	CPB/NIMH
	S.P. James	Clinical Associate	CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

In our previous study of partial sleep deprivation (PSD), we considered both the timing of sleep and the duration of sleep as potential factors in determining response to treatment (annual report Z01 MH 0221-02 CP). We found that the clinical response to sleep deprivation was proportional to the reduction in sleep, and in particular REM sleep. The timing of sleep also appeared to be a factor with patients showing significantly greater improvement when sleep deprived in the second half of the night (PSD-L) than in the first half of the night (PSD-E). The effect of timing on the PSD response was confounded by the fact that patients sleep significantly less on the PSD-L condition. An additional finding of this study was that the antidepressant response to a single night of PSD could be extended by repeating the procedure for a second night.

In our present study, we are comparing the relative effects of PSD-L and PSD-E with the duration of sleep rigidly controlled. In a second study, we are assessing the cumulative antidepressant efficacy of PSD performed over a three week period. Six subjects have been studies to date. Our data is not sufficient to determine the relative efficacy of the two treatments but we have succeeded in achieving comparable sleep reductions on the two treatments. In the longitudinal study of PSD, two patients improved, one with complete remission of her depression, and four showing essentially no change with treatment. A larger sample will be required to establish whether PSD has sustained antidepressant effects in depression.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02202-04 CP

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(60 characters or less. Title must fit on one line between the borders.)*
Clinical Features of Seasonal Affective Disorder (SAD)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	N. E. Rosenthal	Chief, Outpatient Services	CPB/NIMH
Others:	D. A. Sack	Chief, Inpatient Services	CPB/NIMH
	F. M. Jacobsen	Clinical Associate	CPB/NIMH
	S. P. James	Clinical Associate	CPB/NIMH
	B. L. Parry	Clinical Associate	CPB/NIMH
	T. A. Wehr	Chief, Clinical Psychobiology Branch	CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	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.)*

No progress has been made in this area over the past year. We are currently embarking on a study of patients who become depressed during the summer months. This project will be discussed in this section of next year's annual report.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02202-04 CP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Clinical Features of Seasonal Affective Disorder (SAD)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	N. E. Rosenthal	Chief, Outpatient Services	CPB/NIMH
Others:	D. A. Sack	Chief, Inpatient Services	CPB/NIMH
	F. M. Jacobsen	Clinical Associate	CPB/NIMH
	S. P. James	Clinical Associate	CPB/NIMH
	B. L. Parry	Clinical Associate	CPB/NIMH
	T. A. Wehr	Chief, Clinical Psychobiology Branch	CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	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.)*

No progress has been made in this area over the past year. We are currently embarking on a study of patients who become depressed during the summer months. This project will be discussed in this section of next year's annual report.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02203-04 CP

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Sleep, Temperature and Activity Changes in Women with Premenstrual Syndrome

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	T. A. Wehr	Chief, Clinical Psychobiology Branch	CPB/NIMH
Others:	B. L. Parry	Clinical Associate	CPB/NIMH
	W. B. Mendelson	Chief, Unit on Sleep Studies	CPB/NIMH
	N. E. Rosenthal	Chief, Outpatient Studies	CPB/NIMH
	D. A. Sack	Chief, Inpatient Services	CPB/NIMH
	S. P. James	Clinical Associate	CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.25	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.)*

This project has been terminated. Study was finished and key investigator has left area.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02203-04 CP

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Sleep, Temperature and Activity Changes in Women with Premenstrual Syndrome

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	T. A. Wehr	Chief, Clinical Psychobiology Branch	CPB/NIMH
Others:	B. L. Parry	Clinical Associate	CPB/NIMH
	W. B. Mendelson	Chief, Unit on Sleep Studies	CPB/NIMH
	N. E. Rosenthal	Chief, Outpatient Studies	CPB/NIMH
	D. A. Sack	Chief, Inpatient Services	CPB/NIMH
	S. P. James	Clinical Associate	CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.5	0.25	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.)*

This project has been terminated. Study was finished and key investigator has left area.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02205-04 CP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Effects of Light Interventions in Seasonal Affective Disorder (SAD)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	N. E. Rosenthal	Chief, Outpatient Services	CPB/NIMH
Others:	F. M. Jacobsen	Clinical Associate	CPB/NIMH
	R. G. Skwerer	Clinical Associate	CPB/NIMH
	D. A. Sack	Clinical Associate	CPB/NIMH
	T. A. Wehr	Clinical Associate	CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.5	1.5	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.)*

In previous years we have shown that seasonal affective disorder (SAD), a condition characterized by regular fall-winter depressions alternating with depression-free Operiods in the spring and summer, can be treated by exposure to bright artificial light. We have shown that this effect does not depend on sleep deprivation and that light does not have to be given during the dark part of the 24-hour day. This year we have continued to explore the properties of phototherapy in three separate studies. We have shown in 10 SAD patients that four hours of bright light treatment in the evening is significantly more effective if the eyes are exposed than if the skin is exposed. This suggests that the initial receptors for the phototherapy effect are in the eyes rather than the skin. In 16 other SAD patients we have shown that two hours of bright light is equally effective if presented in the morning and the middle of the day. This finding argues against a current theory that light exerts its antidepressant effects by resettig circadian rhythms, and also has practical relevance for patients, who frequently find that it is more convenient to receive treatment during the day than in the early morning hours. UIn a final study we have shown that two hours of bright light treatment in the morning hours. In a final study we have shown that two hours of bright light treatment in the morning has no mood-altering effect in 11 carefully screened normal volunteers, which suggests that our findings in SAD patients cannot be generalized to all segments of the population.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02205-04 CP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Effects of Light Interventions in Seasonal Affective Disorder (SAD)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	N. E. Rosenthal	Chief, Outpatient Services	CPB/NIMH
Others:	F. M. Jacobsen	Clinical Associate	CPB/NIMH
	R. G. Skwerer	Clinical Associate	CPB/NIMH
	D. A. Sack	Clinical Associate	CPB/NIMH
	T. A. Wehr	Clinical Associate	CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.5	1.5	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.)*

In previous years we have shown that seasonal affective disorder (SAD), a condition characterized by regular fall-winter depressions alternating with depression-free Operiods in the spring and summer, can be treated by exposure to bright artificial light. We have shown that this effect does not depend on sleep deprivation and that light does not have to be given during the dark part of the 24-hour day. This year we have continued to explore the properties of phototherapy in three separate studies. We have shown in 10 SAD patients that four hours of bright light treatment in the evening is significantly more effective if the eyes are exposed than if the skin is exposed. This suggests that the initial receptors for the phototherapy effect are in the eyes rather than the skin. In 16 other SAD patients we have shown that two hours of bright light is equally effective if presented in the morning and the middle of the day. This finding argues against a current theory that light exerts its antidepressant effects by resettig circadian rhythms, and also has practical relevance for patients, who frequently find that it is more convenient to receive treatment during the day than in the early morning hours. UIn a final study we have shown that two hours of bright light treatment in the morning hours. In a final study we have shown that two hours of bright light treatment in the morning has no mood-altering effect in 11 carefully screened normal volunteers, which suggests that our findings in SAD patients cannot be generalized to all segments of the population.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02206-04 CP

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Neurobiology of Seasonal Affective Disorders (SAD)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	N.E. Rosenthal	Chief, Outpatient Services	CPB/NIMH
Others:	F.M. Jacobsen	Clinical Associate	CPB/NIMH
	R.G. Skwerer	Clinical Associate	CPB/NIMH
	D.A. Sack	Clinical Associate	CPB/NIMH
	T.A. Wehr	Clinical Associate	CPB/NIMH
	L. Tamakin	Research Biologist	CPB/NIMH

COOPERATING UNITS *(if any)*

C. Duncan	Chief, Unit on Psychophysiology
M. Rudorfer	Senior Staff, SCP/LCS
M. Linnoila	Clinical Director, DICBR/NIAAA

LAB/BRANCH
Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

Despite the prominent clinical changes seen in seasonal affective disorder (SAD), our knowledge of biological markers of this condition has previously been confined to hypersomnia in the winter with a tendency to reduced slow wave sleep. We have not previously shown any biological correlates of the dramatic antidepressant effects of phototherapy. This past year we have shown that during the winter patients with SAD show elevated plasma prolactin (N=10) and thyroxine levels (N=20) compared to normal controls. Preliminary results also suggest a reduced level of the serotonin and dopamine metabolites, 5-HIAA and HVA in the CSF, as compared with non-seasonally depressed patients. Light treatment is associated with at least two objective biological changes: (1) an increase in the P300 component of the event response potential in response to visual but not auditory stimuli. This increase is proportional to the degree of antidepressant response ($r=0.85$, $P<.02$); and (2) a reduction in the responsiveness of lymphocytes to mitogen stimulation. We plan to expand our number of subjects and extend these findings next year.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02206-04 CP

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Neurobiology of Seasonal Affective Disorders (SAD)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	N.E. Rosenthal	Chief, Outpatient Services	CPB/NIMH
Others:	F.M. Jacobsen	Clinical Associate	CPB/NIMH
	R.G. Skwerer	Clinical Associate	CPB/NIMH
	D.A. Sack	Clinical Associate	CPB/NIMH
	T.A. Wehr	Clinical Associate	CPB/NIMH
	L. Tamakin	Research Biologist	CPB/NIMH

COOPERATING UNITS *(if any)*

	C. Duncan	Chief, Unit on Psychophysiology
	M. Rudorfer	Senior Staff, SCP/LCS
	M. Linnoila	Clinical Director, DICBR/NIAAA

LAB/BRANCH
Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

Despite the prominent clinical changes seen in seasonal affective disorder (SAD), our knowledge of biological markers of this condition has previously been confined to hypersomnia in the winter with a tendency to reduced slow wave sleep. We have not previously shown any biological correlates of the dramatic antidepressant effects of phototherapy. This past year we have shown that during the winter patients with SAD show elevated plasma prolactin (N=10) and thyroxine levels (N=20) compared to normal controls. Preliminary results also suggest a reduced level of the serotonin and dopamine metabolites, 5-HIAA and HVA in the CSF, as compared with non-seasonally depressed patients. Light treatment is associated with at least two objective biological changes: (1) an increase in the P300 component of the event response potential in response to visual but not auditory stimuli. This increase is proportional to the degree of antidepressant response ($r=0.85$, $P<.02$); and (2) a reduction in the responsiveness of lymphocytes to mitogen stimulation. We plan to expand our number of subjects and extend these findings next year.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02221-03 CP

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Effects of Melatonin in Seasonal Affective Disorder (SAD)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	N. E. Rosenthal	Chief, Outpatient Services	CPB/NIMH
Others:	D. A. Sack	Chief, Inpatient Services	CPB/NIMH
	F. M. Jacobsen	Clinical Associate	CPB/NIMH
	S. P. James	Clinical Associate	CPB/NIMH
	B. L. Parry	Clinical Associate	CPB/NIMH
	T. A. Wehr	Chief, Clinical Psychobiology Branch	CPB/NIMH
	W. B. Mendelson	Chief, Unit on Sleep Studies	CPB/NIMH
	L. Tamarkin	Research Biologist	CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.4	0.8	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 results of four separate studies in which we investigated the role of melatonin in SAD and phototherapy suggest that its role is not of central importance. Although we shall continue to measure the secretion of melatonin and its metabolites in plasma and urine, these investigations do not warrant a separate report at this time but will be used in the report on "Neurobiology of Seasonal Affective Disorder (SAD) #Z01 MH 022206-04 CP. We are therefore terminating this section of our annual report.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02221-03 CP

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Effects of Melatonin in Seasonal Affective Disorder (SAD)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	N. E. Rosenthal	Chief, Outpatient Services	CPB/NIMH
Others:	D. A. Sack	Chief, Inpatient Services	CPB/NIMH
	F. M. Jacobsen	Clinical Associate	CPB/NIMH
	S. P. James	Clinical Associate	CPB/NIMH
	B. L. Parry	Clinical Associate	CPB/NIMH
	T. A. Wehr	Chief, Clinical Psychobiology Branch	CPB/NIMH
	W. B. Mendelson	Chief, Unit on Sleep Studies	CPB/NIMH
	L. Tamarkin	Research Biologist	CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.4	0.8	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 results of four separate studies in which we investigated the role of melatonin in SAD and phototherapy suggest that its role is not of central importance. Although we shall continue to measure the secretion of melatonin and its metabolites in plasma and urine, these investigations do not warrant a separate report at this time but will be used in the report on "Neurobiology of Seasonal Affective Disorder (SAD) #Z01 MH 022206-04 CP. We are therefore terminating this section of our annual report.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02222-03 CP

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
The Treatment of Rapid-Cycling Manic-Depressive with Thyroxine

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D.A. Sack	Chief, Inpatient Services	CPB/NIMH
Others:	T.A. Wehr	Chief, Clinical Psychobiology Branch	CPB/NIMH
	N.E. Rosenthal	Chief, Outpatient Services	CPB/NIMH
	B.L. Parry	Clinical Associate	CPB/NIMH
	W.B. Mendelson	Chief, Unit on Sleep Studies	CPB/NIMH
	S.P. James	Clinical Associate	CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3	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.)*

Disturbances in thhypothalamic-pituitary-thyroid axis (HPT) may have an etiologic role in patients with depression. Patients with very frequent recurrences and a tendency to go from mania to depression or vice-versa with only a brief intervening period of euthymic mood (rapid-cyclers) may suffer from an extreme form of this HPT disturbance seen in other depressives as indicated by tendency to develop frank and subclinical hypothyroism when treated with lithium carbonate.

In the interval since our previous report, we have observed that the clinical response to thyroxine appears to be of relatively short duration (<6 months) and that relapse does not appear to be clearly related to decreases in thyroid hormones. Increases in doses resulted in partial clinical improvement in one case.

Our preliminary results suggest that: (1) patients with very rapid mood cyclers are most likely to show improvement with thyroxine therapy, (2) clinical improvement was found only with hypermetabolic doses of thyroxine, (3) the duration of the response to thyroxine appears to be brief.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02222-03 CP

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
The Treatment of Rapid-Cycling Manic-Depressive with Thyroxine

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D.A. Sack	Chief, Inpatient Services	CPB/NIMH
Others:	T.A. Wehr	Chief, Clinical Psychobiology Branch	CPB/NIMH
	N.E. Rosenthal	Chief, Outpatient Services	CPB/NIMH
	B.L. Parry	Clinical Associate	CPB/NIMH
	W.B. Mendelson	Chief, Unit on Sleep Studies	CPB/NIMH
	S.P. James	Clinical Associate	CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3	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.)*

Disturbances in thhypothalamic-pituitary-thyroid axis (HPT) may have an etiologic role in patients with depression. Patients with very frequent recurrences and a tendency to go from mania to depression or vice-versa with only a brief intervening period of euthymic mood (rapid-cyclers) may suffer from an extreme form of this HPT disturbance seen in other depressives as indicated by tendency to develop frank and subclinical hypothyroism when treated with lithium carbonate.

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Our preliminary results suggest that: (1) patients with very rapid mood cyclers are most likely to show improvement with thyroxine therapy, (2) clinical improvement was found only with hypermetabolic doses of thyroxine, (3) the duration of the response to thyroxine appears to be brief.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02223-03-CP

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Pentobarbital and Ethanol Toxicity: Relation to the Benzodiazepine Receptor

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	W. B. Mendelson	Chief, Section on Sleep Studies	CPB/NIMH
Others:	J. V. Martin	Staff Fellow	CPB/NIMH
	R. Wagner	Guest Worker	CPB/NIMH

COOPERATING UNITS *(if any)*
LBC/NIADDK
Rockland Research Institute

LAB/BRANCH
Clinical Psychobiology Branch

SECTION
Section on Sleep Studies

INSTITUTE AND LOCATION
NIMH,NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

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.)*

Because of reports that both barbiturates and ethanol interact with the GABA-benzodiazepine-Chloride channel complex, we embarked on a series of studies to determine if agents which block various aspects of the complex might reduce toxicity from high doses of these sedatives. We previously reported on two chloride channel blockers (IPPO and TBPS) which can reduce mortality due to pentobarbital in mice and have relatively low toxicities when given alone. We have begun to study respiration in rats as a possible cause of the lethal effects of sedatives. We found dose-dependent decreases in respiration rate with both pentobarbital and flurazepam. We are currently studying the effects of chloride channel blockers on this depression of respiration.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02223-03-CP

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Pentobarbital and Ethanol Toxicity: Relation to the Benzodiazepine Receptor

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	W. B. Mendelson	Chief, Section on Sleep Studies	CPB/NIMH
Others:	J. V. Martin	Staff Fellow	CPB/NIMH
	R. Wagner	Guest Worker	CPB/NIMH

COOPERATING UNITS *(if any)*
LBC/NIADDK
Rockland Research Institute

LAB/BRANCH
Clinical Psychobiology Branch

SECTION
Section on Sleep Studies

INSTITUTE AND LOCATION
NIMH,NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

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.)*

Because of reports that both barbiturates and ethanol interact with the GABA-benzodiazepine-Chloride channel complex, we embarked on a series of studies to determine if agents which block various aspects of the complex might reduce toxicity from high doses of these sedatives. We previously reported on two chloride channel blockers (IPPO and TBPS) which can reduce mortality due to pentobarbital in mice and have relatively low toxicities when given alone. We have begun to study respiration in rats as a possible cause of the lethal effects of sedatives. We found dose-dependent decreases in respiration rate with both pentobarbital and flurazepam. We are currently studying the effects of chloride channel blockers on this depression of respiration.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02225-03-CP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Studies in the Role of Calcium Flux in the Sleep-Inducing Effects on Flurazepam

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	W. B. Mendelson	Chief, Section on Sleep Studies	CPB/NIMH
Others:	J. V. Martin	Staff Fellow	CPB/NIMH
	R. Wagner	Guest Worker	CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

Section on Sleep Studies

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

Our previous studies have shown that there may be a functional relationship between benzodiazepine (BZ) receptor stimulation and alterations in calcium flux. Nifedipine, a calcium channel blocker, prevented the sleep-inducing effects of flurazepam in rats. Conversely, as we reported last year, a calcium channel agonist (Bay K 8644) potentiates the effects of flurazepam. This year we have examined the specificity of the effects of nifedipine with respect to other actions of BZ. Nifedipine did not block the effects of diazepam in increasing punished drinking in a model for anxiolytic effects of drugs. Nifedipine also did not block anticonvulsant effects of diazepam. Calcium channels may play a more important role in sleep induction than in other actions of BZ. We also showed that sleep-inducing effects of pentobarbital were not susceptible to blockade by nifedipine, indicating that the role of calcium channels in sleep may be specific for BZ; that is, barbiturates may cause sleep through a mechanism that does not require changes in Ca^{2+} flux.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02225-03-CP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Studies in the Role of Calcium Flux in the Sleep-Inducing Effects on Flurazepam

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	W. B. Mendelson	Chief, Section on Sleep Studies	CPB/NIMH
Others:	J. V. Martin	Staff Fellow	CPB/NIMH
	R. Wagner	Guest Worker	CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

Section on Sleep Studies

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

Our previous studies have shown that there may be a functional relationship between benzodiazepine (BZ) receptor stimulation and alterations in calcium flux. Nifedipine, a calcium channel blocker, prevented the sleep-inducing effects of flurazepam in rats. Conversely, as we reported last year, a calcium channel agonist (Bay K 8644) potentiates the effects of flurazepam. This year we have examined the specificity of the effects of nifedipine with respect to other actions of BZ. Nifedipine did not block the effects of diazepam in increasing punished drinking in a model for anxiolytic effects of drugs. Nifedipine also did not block anticonvulsant effects of diazepam. Calcium channels may play a more important role in sleep induction than in other actions of BZ. We also showed that sleep-inducing effects of pentobarbital were not susceptible to blockade by nifedipine, indicating that the role of calcium channels in sleep may be specific for BZ; that is, barbiturates may cause sleep through a mechanism that does not require changes in Ca^{2+} flux.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02290-02 CP

PERIOD COVERED
October 1, 1985 to September 30, 1986

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

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	L. Tamarkin	Research Biologist	CPB/NIMH
Others:	G. Paciotti	Biologist	CPB/NIMH

COOPERATING UNITS *(if any)*
J. Nurnberger, Biological Psychiatry Branch, NIMH
C. May, Laboratory of Neurosciences, NIA
E. Oldfield, Surgical Neurology, NINCDS

LAB/BRANCH
Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.4	.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.)*

Plasma melatonin profiles over one or 2 days, or at night have been determined in a variety of patients and normal volunteers. Assessment of circulating melatonin during the summer and winter, during exposure to light at night, during nocturnal wandering, and in comparison to cerebrospinal fluid melatonin levels were the specific questions asked this past year.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02291-02 CP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Site of Action of Melatonin

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	L. Tamarkin	Research Biologist	CPB/NIMH
Others:	G. Paciotti	Biologist	CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

Despite intense effort to conclusively determine the mechanism of action of the pineal hormone melatonin, I feel that the data are not sufficiently reproducible, suggesting that there is a variable(s) in our systems that is not controlled or that the positive data are artifactual. These studies were inconclusive and were terminated.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02291-02 CP

PERIOD COVERED
October 1, 1985 to September 30, 1986

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

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	L. Tamarkin	Research Biologist	CPB/NIMH
Others:	G. Paciotti	Biologist	CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

Despite intense effort to conclusively determine the mechanism of action of the pineal hormone melatonin, I feel that the data are not sufficiently reproducible, suggesting that there is a variable(s) in our systems that is not controlled or that the positive data are artifactual. These studies were inconclusive and were terminated.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02292-02 CP

PERIOD COVERED: October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Melatonin Effect on Horomone-stimulated Cell Growth.

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	L. Tamarkin	Research Biologist	CPB/NIMH
Others:	G. Paciotti	Biologist	CPB/NIMH

COOPERATING UNITS *(if any)*: David N. Danforth, Surgery Branch, NCI

LAB/BRANCH: Clinical Psychobiology Branch

SECTION:

INSTITUTE AND LOCATION: NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.1	.1	

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.)*

Physiologic concentrations of melatonin have been shown by us to increase estrogen receptor concentrations in vitro in a human breast cancer cell line. This occurs within 40 to 60 minutes. We determined the rapid effects of melatonin on 2-day MCF-7 cell growth. The long-term effects of melatonin on MCF-7 cell growth was assessed by implanting tumor cells in athymic, nude mice. The present data fail to demonstrate any acute change in growth by melatonin, but are suggestive for a long-term inhibitory effect of melatonin on MCF-7 cell growth in nude mice.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02292-02 CP

PERIOD COVERED: October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Melatonin Effect on Horomone-stimulated Cell Growth.

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	L. Tamarkin	Research Biologist	CPB/NIMH
Others:	G. Paciotti	Biologist	CPB/NIMH

COOPERATING UNITS *(if any)*: David N. Danforth, Surgery Branch, NCI

LAB/BRANCH: Clinical Psychobiology Branch

SECTION:

INSTITUTE AND LOCATION: NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

Physiologic concentrations of melatonin have been shown by us to increase estrogen receptor concentrations in vitro in a human breast cancer cell line. This occurs within 40 to 60 minutes. We determined the rapid effects of melatonin on 2-day MCF-7 cell growth. The long-term effects of melatonin on MCF-7 cell growth was assessed by implanting tumor cells in athymic, nude mice. The present data fail to demonstrate any acute change in growth by melatonin, but are suggestive for a long-term inhibitory effect of melatonin on MCF-7 cell growth in nude mice.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02294-02 CP

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Antidepressant Phamacology of the Rodent Circadian System

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	W. C. Duncan	Research Psychologist	CPB/NIMH
Others:	L. Tamarkin	Research Biologist	CPB/NIMH
	T. A. Wehr	Chief, Clinical Psychobiology Branch	CPB/NIMH
	P. G. Sokolove	Professorm of Biological Sciences	UMBC

COOPERATING UNITS *(if any)*
University of Maryland, Baltimore County (UMBC)

LAB/BRANCH
Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

Disruptions of the sleep-wake cycle are a major symptom of major affective illness; these disturbances can be characterized by their specific temporal pattern such as early, middle or late insomnia. In addition, temporal abnormalities in certain physiological processes such as the core body temperature rhythm or cortisol release often accompany these sleep disturbances. In general these deficits can be related to a) pathological changes in the frequency of a central circa- dian pacemaker or b) pathological temporal phase relationships between the central pacemaker and physiological processes controlled by the clock (such as the rest-activity cycle). Briefly stated, our hypothesis is that chemical antidepressants restore more normal frequency or phase relationships, and therefore exhibit antidepressant properties. We have therefore been investigating the effects of the MAOI antidepressant clorgyline on these parameters of the vertebrate circadian system.

In agreement with the phase advance hypothesis, in the Syrian hamster we have observed that clorgyline slows the frequency of the circadian clock; this is the first compelling demonstration of MAOI input to the central mammalian pacemaker. Secondly, consistent with its delayed therapeutic effects, clorgyline does not alter the normal phase relationship between the central clock and the rest-activity cycle. Finally, this compound produces an increase in the activity -rest ratio, and a decrease in body mass. We are currently investigating the behavioral and physiological mechanisms responsible for these effects.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02294-02 CP

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
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PI:	W. C. Duncan	Research Psychologist	CPB/NIMH
Others:	L. Tamarkin	Research Biologist	CPB/NIMH
	T. A. Wehr	Chief, Clinical Psychobiology Branch	CPB/NIMH
	P. G. Sokolove	Professorm of Biological Sciences	UMBC

COOPERATING UNITS *(if any)*
University of Maryland, Baltimore County (UMBC)

LAB/BRANCH
Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

Disruptions of the sleep-wake cycle are a major symptom of major affective illness; these disturbances can be characterized by their specific temporal pattern such as early, middle or late insomnia. In addition, temporal abnormalities in certain physiological processes such as the core body temperature rhythm or cortisol release often accompany these sleep disturbances. In general these deficits can be related to a) pathological changes in the frequency of a central circa- dian pacemaker or b) pathological temporal phase relationships between the central pacemaker and physiological processes controlled by the clock (such as the rest-activity cycle). Briefly stated, our hypothesis is that chemical antidepressants restore more normal frequency or phase relationships, and therefore exhibit antidepressant properties. We have therefore been investigating the effects of the MAOI antidepressant clorgyline on these parameters of the vertebrate circadian system.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02303-01-CP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Studies of Sleep in Psychiatric Illness

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: W. B. Mendelson Chief, Section on Sleep Studies CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

Section on Sleep Studies

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

Sleep studies of 8 affective disorder patients (7 bipolar and 1 unipolar) revealed many of the stigmata of depression including poor sleep efficiency and shorter total sleep, but had normal REM latency. Frequency analysis of the EEG showed the expected decline across REM-nonREM cycles, but there was no significant difference between patients and controls.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02303 -01--CP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Studies of Sleep in Psychiatric Illness

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: W. B. Mendelson Chief, Section on Sleep Studies CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

Section on Sleep Studies

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

Sleep studies of 8 affective disorder patients (7 bipolar and 1 unipolar) revealed many of the stigmata of depression including poor sleep efficiency and shorter total sleep, but had normal REM latency. Frequency analysis of the EEG showed the expected decline across REM-nonREM cycles, but there was no significant difference between patients and controls.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02324-01 CP

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Neuroendocrine modulation of cellular immune response

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	L. Tamarkin	CPB/NIMH
Others:	G. Paciotti, Biologist	CPB/NIMH
	R. Bernardini, Fogarty Fellow	CPB/NIMH
	R. Skwerer, Clinical Associate	CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

We have initiated a series of investigations to determine the impact of some neuroendocrine challenges on the immune system. Two pharmacologic stress tests were performed on rats and the acute (4h) effect on splenic lymphocytes was determined. We have observed that the B-adrenergic agonist, isoproterenol, suppressed responses of lymphcyte to mitogen stimulation. This inhibitory effect of isoproterenol on lymphocytes is not due to direct effects of isoproterenol, but may be directly related to the presence of the adrenal gland (adrenalectomized animals injected with isoproterenol did not exhibit suppression of lymphocyte activity). Further in vitro studies demonstrated a direct suppressive effect of the glucocorticoid agonist, dexamethasone and this suppressive effect may be mediated through the phosphatidylinositol cycle (the phorbol ester, PMA, a stiumlator of protein kihase C, inhibits lymphocyte activity.) The second stress test was insulin induced hypoglycemia. Lowering of blood glucose over a 4-h period caused a marked suppression in lymphocyte activity. Thus, the acute effect of pharmacologic stress is to inhibit lymphocyte activity. Studies are in progress to determine the effect of chronic pharmacologic stress on lymphocyte activity.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02324-01 CP

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Neuroendocrine modulation of cellular immune response

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	L. Tamarkin	CPB/NIMH
Others:	G. Paciotti, Biologist	CPB/NIMH
	R. Bernardini, Fogarty Fellow	CPB/NIMH
	R. Skwerer, Clinical Associate	CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

We have initiated a series of investigations to determine the impact of some neuroendocrine challenges on the immune system. Two pharmacologic stress tests were performed on rats and the acute (4h) effect on splenic lymphocytes was determined. We have observed that the B-adrenergic agonist, isoproterenol, suppressed responses of lymphcyte to mitogen stimulation. This inhibitory effect of isoproterenol on lymphocytes is not due to direct effects of isoproterenol, but may be directly related to the presence of the adrenal gland (adrenalectomized animals injected with isoproterenol did not exhibit suppression of lymphocyte activity). Further in vitro studies demonstrated a direct suppressive effect of the glucocorticoid agonist, dexamethasone and this suppressive effect may be mediated through the phosphatidylinositol cycle (the phorbol ester, PMA, a stiumlator of protein kihase C, inhibits lymphocyte activity.) The second stress test was insulin induced hypoglycemia. Lowering of blood glucose over a 4-h period caused a marked suppression in lymphocyte activity. Thus, the acute effect of pharmacologic stress is to inhibit lymphocyte activity. Studies are in progress to determine the effect of chronic pharmacologic stress on lymphocyte activity.

GPO 914-916

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02325-01 CP

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Light and lymphocyte activity: basic and clinical studies

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	L. Tamarkin, Research Biologist	CPB/NIMH
Others:		
	G. Paciotti, Biologist	CPB/NIMH
	R. Bernardini, Fogarty Fellow	CPB/NIMH
	R. Skwerer, Clinical Associate	CPB/NIMH
	N. Rosenthal, M.D.	CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.4	.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.)*

Light has been shown to positively affect mood in a population of patients who get depressed in the winter. For light to have a positive response, the patient must be exposed to bright light (3000lux) for a few hours each day. During this past year we sampled patients "on" or "off" light therapy to assess peripheral blood lymphocyte activity during these two conditions. Curiously, lymphocyte activity was significantly suppressed when they were "on" light treatment, and showed an improvement in mood.

Based on these observations we exposed rats to the same bank of light for a week. Splenic lymphocyte activity was markedly elevated following this chronic exposure to light. However, 4-h exposure to light suppressed lymphocyte activity. These data suggest that light may directly or indirectly affect the immune system.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02325-01 CP

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Light and lymphocyte activity: basic and clinical studies

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI: L. Tamarkin, Research Biologist — CPB/NIMH

Others:

G. Paciotti, Biologist — CPB/NIMH
R. Bernardini, Fogarty Fellow — CPB/NIMH
R. Skwerer, Clinical Associate — CPB/NIMH
N. Rosenthal, M.D. — CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.4	.4	

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.)*

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02326-01 CP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Behavioral modulation of the cellular immune response

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	L. Tamarkin	Research Biologist	CPB/NIMH
Others:	G. Paciotti	Biologist	CPB/NIMH
	R. Bernardini	Fogarty Fellow	CPB/NIMH
	R. Skwerer	Clinical Associate	CPB/NIMH

COOPERATING UNITS *(if any)*

S. Suomi, Laboratory of Comparative Etyhology, NICHD

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

Young rhesus monkeys are currently being introduced to a novel environment at the Poolesville Animal Facility. Dr. Suomi has designed a strategy to create optimal troop size with a minimum of social conflicts. This requires discrete pairings of animals into larger and larger groups. We are collecting plasma and peripheral blood lymphoctyes during specific intervals. We have observed that one animal, the behaviorally dominant individual, has higher lymphocyte activity than the other 3 in the group. This has held for two groups of 4 animals. During the course of behavioral stress challenges we have also observed that "group" lymphocyte activity is initially suppressed, rebounds and returns to baseline.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02326-01 CP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Behavioral modulation of the cellular immune response

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	L. Tamarkin	Research Biologist	CPB/NIMH
Others:	G. Paciotti	Biologist	CPB/NIMH
	R. Bernardini	Fogarty Fellow	CPB/NIMH
	R. Skwerer	Clinical Associate	CPB/NIMH

COOPERATING UNITS *(if any)*

S. Suomi, Laboratory of Comparative Etyhology, NICHD

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

Young rhesus monkeys are currently being introduced to a novel environment at the Poolesville Animal Facility. Dr. Suomi has designed a strategy to create optimal troop size with a minimum of social conflicts. This requires discrete pairings of animals into larger and larger groups. We are collecting plasma and peripheral blood lymphoctyes during specific intervals. We have observed that one animal, the behaviorally dominant individual, has higher lymphocyte activity than the other 3 in the group. This has held for two groups of 4 animals. During the course of behavioral stress challenges we have also observed that "group" lymphocyte activity is initially suppressed, rebounds and returns to baseline.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02327-01 CP

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Direct effect of lymphokines on cultured human breast cancer cells.

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	L. Tamarkin	Research Biologist	CPB/NIMH
Others:	G. Paciotti	Biologist	CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.6	.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.)*

Human breast cancer cells, MCF-7, were grown in vitro for 2 days in the presence or absence of various doses of interleukin-2 or interleukin-1. Both of these lymphokines have direct effects on the growth of MCF-7 cells. Interleukin-1 has a strictly inhibitory effect on growth, while interleukin-2 has a biphasic effect. At high doses IL-2 inhibits MCF-7 cell growth while at low doses IL-2 actually enhances tumor cell growth.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02327-01 CP

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
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PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	L. Tamarkin	Research Biologist	CPB/NIMH
Others:	G. Paciotti	Biologist	CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.6	.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.)*

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02328-01 CP

PERIOD COVERED

October 1, 1985 to September 30. 1986

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

Direct effects of IL-2 on cultured anterior pituitaries

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	L. Tamarkin	Research Biologist	CPB/NIMH
Others:	G. Paciotti	Biologist	CPB/NIMH
	R. Bernardini	Fogarty Fellow	CPB/NIMH
	R. Skwerer	Clinical Associate	CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.5	.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.)*

Our working hypothesis is that lymphokines and in particular interleukin-2 (IL-2) may affect pituitary hormone release. The pituitary hormone, adrenocorticotropin (ACTH) was our first candidate to be modulated by IL-2. The adrenal steroids inhibit lymphocyte function so we reasoned that IL-2 might feedback positively releasing ACTH and dampening lymphocyte activity. This may be a homestatic feedback loop between the pituitary and the immune system. The simplest system to test this hypothesis was in vitro. Preliminary results indicate that mouse IL-2 caused a significant release of ACTH in vitro. Further investigations are required to determine if the ACTH released by IL2 is specific and to test IL-2 action on other neuroendocrine tissue.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02328-01 CP

PERIOD COVERED
October 1, 1985 to September 30 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Direct effects of IL-2 on cultured anterior pituitaries

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	L. Tamarkin	Research Biologist	CPB/NIMH
Others:	G. Paciotti	Biologist	CPB/NIMH
	R. Bernardini	Fogarty Fellow	CPB/NIMH
	R. Skwerer	Clinical Associate	CPB/NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION
NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.5	.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.)*

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02329-01 CP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Relationship Between Eating & Mood in S.A.D.

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	N.E. Rosenthal	Chief, Outpatient Services	CPB/NIMH
Others:	F.M. Jacobsen	Clinical Associate	CPB/NIMH
	R.G. Skwerer	Clinical Associate	CPB/NIMH
	D.A. Sack	Clinical Associate	CPB/NIMH
	T.A. Wehr	Clinical Associate	CPB/NIMH
	M. Genhart	Clinical Associate	CPB/NIMH

COOPERATING UNITS *(if any)*

B. Caballero	Dept. of Endocrinology & Metabolism, MIT
J.J. Wurtman	Dept. of Endocrinology & Metabolism, MIT
B.T. Spring	Prof. Dept. of Psychology, Texas Tech.

LAB/BRANCH

Clinical Psychobiology Branch

SECTION

INSTITUTE AND LOCATION

NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

Patients with SAD undergo major seasonal changes in eating behavior and generally overeat, crave carbohydrates and gain weight in the fall and winter. In order to explore this relationship, 16 patients with SAD and 16 age- and sex-matched controls were given tow isocaloric lunches on two different days: a high-carbohydrate meal and a high-protein meal. Mood measurements (Profile of Mood States, POMS) taken before and after the meal indicated that both SAD patients and normals reported reduced levels of tension ($P<.01$), depression ($P<.02$) and anger ($P<.05$) following the high-carbohydrate versus the high-protein meal. However, normals reported increased fatigue after a high-carbohydrate versus the high-protein meal. However, normals reported increased fatigue after a high-carbohydrate meal whereas patients showed decreased fatigue levels ($P<.05$). These data suggest that carbohydrate craving in SAD may be part of a complex behavioral-biochemical feedback loop involving homeostatic regulation of brain chemistry, which presumably varies seasonally. The seasonal changes in eating and fat deposition in SAD patients may be part of an overall seasonal rhythm in energy utilization. Such rhythms occur in other animals, which may serve as useful models for further studies of SAD.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02329-01 CP

PERIOD COVERED: October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Relationship Between Eating & Mood in S.A.D.

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	N.E. Rosenthal	Chief, Outpatient Services	CPB/NIMH
Others:	F.M. Jacobsen	Clinical Associate	CPB/NIMH
	R.G. Skwerer	Clinical Associate	CPB/NIMH
	D.A. Sack	Clinical Associate	CPB/NIMH
	T.A. Wehr	Clinical Associate	CPB/NIMH
	M. Genhart	Clinical Associate	CPB/NIMH

COOPERATING UNITS *(if any)*

	B. Caballero	Dept. of Endocrinology & Metabolism, MIT
	J.J. Wurtman	Dept. of Endocrinology & Metabolism, MIT
	B.T. Spring	Prof. Dept. of Psychology, Texas Tech.

LAB/BRANCH: Clinical Psychobiology Branch

SECTION:

INSTITUTE AND LOCATION: NIMH, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	0.5	1.0

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.)*

Patients with SAD undergo major seasonal changes in eating behavior and generally overeat, crave carbohydrates and gain weight in the fall and winter. In order to explore this relationship, 16 patients with SAD and 16 age- and sex-matched controls were given tow isocaloric lunches on two different days: a high-carbohydrate meal and a high-protein meal. Mood measurements (Profile of Mood States, POMS) taken before and after the meal indicated that both SAD patients and normals reported reduced levels of tension ($P<.01$), depression ($P<.02$) and anger ($P<.05$) following the high-carbohydrate versus the high-protein meal. However, normals reported increased fatigue after a high-carbohydrate versus the high-protein meal. However, normals reported increased fatigue after a high-carbohydrate meal whereas patients showed decreased fatigue levels ($P<.05$). These data suggest that carbohydrate craving in SAD may be part of a complex behavioral-biochemical feedback loop involving homeostatic regulation of brain chemistry, which presumably varies seasonally. The seasonal changes in eating and fat deposition in SAD patients may be part of an overall seasonal rhythm in energy utilization. Such rhythms occur in other animals, which may serve as useful models for further studies of SAD.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00931-13 LGCB

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Characteristics and Regulation of S-Adenosylhomocysteine Hydrolase

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.	P. S. Backlund, Jr.	Senior Staff Fellow	LGCB NIMH
	R. R. Aksamit	Research Chemist	LGCB NIMH
	G. L. Cantoni	Chief, Laboratory of General and Comparative Biochemistry	LGCB NIMH
Others:			
	C. G. Unson	Research Associate, Rockefeller University, NY	

COOPERATING UNITS *(if any)*

Department of Human Biopathology, University of Rome
La Sapienza, Rome, Italy

LAB/BRANCH

Laboratory of General and Comparative Biochemistry

SECTION

Section on Proteins

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

S-adenosylhomocysteine hydrolase plays a critical role in regulating AdoMet-dependent methylations in eukaryotic cells by regulating the ratio of AdoMet/AdoHcy. Several approaches are being used to determine the structure and function of this enzyme.

1) Structure Determination: The enzyme has been purified to homogeneity from rat liver. Conformational changes for active and inactive forms of the enzyme have been examined by fluorescence, circular dichroism, and by photoaffinity labeling of the active sites. Peptide fragments of the protein have been isolated and partial amino acid sequences determined. Oligonucleotide probes from the peptide sequences and antibodies are being used to screen a cDNA library from rat liver to obtain the nucleic acid sequence.

2) Ligand Binding and Kinetic Properties: The role of NAD, nucleotide, and cAMP binding in regulating the catalytic activity has been studied. A large number of adenosine and adenosylhomocysteine analogs have been examined for their ability to function as inhibitors and/or substrates of the enzyme.

3) Biological Effects of Inhibitors: In vivo these adenosine analogs can form very potent and specific inhibitors of transmethylation reactions, and these inhibitors have a wide range of biological activities, including antiviral activity against several RNA and DNA viruses, inhibition of leukocyte chemotaxis, and stimulation of cell differentiation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00931-13 LGCB

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Characteristics and Regulation of S-Adenosylhomocysteine Hydrolase

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.	P. S. Backlund, Jr.	Senior Staff Fellow	LGCB NIMH
	R. R. Aksamit	Research Chemist	LGCB NIMH
	G. L. Cantoni	Chief, Laboratory of General and Comparative Biochemistry	LGCB NIMH
Others:			
	C. G. Unson	Research Associate, Rockefeller University, NY	

COOPERATING UNITS *(if any)*

Department of Human Biopathology, University of Rome
La Sapienza, Rome, Italy

LAB/BRANCH

Laboratory of General and Comparative Biochemistry

SECTION

Section on Proteins

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

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1) Structure Determination: The enzyme has been purified to homogeneity from rat liver. Conformational changes for active and inactive forms of the enzyme have been examined by fluorescence, circular dichroism, and by photoaffinity labeling of the active sites. Peptide fragments of the protein have been isolated and partial amino acid sequences determined. Oligonucleotide probes from the peptide sequences and antibodies are being used to screen a cDNA library from rat liver to obtain the nucleic acid sequence.

2) Ligand Binding and Kinetic Properties: The role of NAD, nucleotide, and cAMP binding in regulating the catalytic activity has been studied. A large number of adenosine and adenosylhomocysteine analogs have been examined for their ability to function as inhibitors and/or substrates of the enzyme.

3) Biological Effects of Inhibitors: In vivo these adenosine analogs can form very potent and specific inhibitors of transmethylation reactions, and these inhibitors have a wide range of biological activities, including antiviral activity against several RNA and DNA viruses, inhibition of leukocyte chemotaxis, and stimulation of cell differentiation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00936-23 LGCB

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Homocystinuria: Methionine Metabolism in Mammals

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

S. H. Mudd Chief, Section on Alkaloid Biosynthesis LGCB NIMH

COOPERATING UNITS *(if any)*

William Gahl Human Genetics Branch Child Health and Human Development NIH

LAB/BRANCH

Laboratory of General and Comparative Biochemistry

SECTION

Section on Alkaloid Biosynthesis

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1/12	1/12	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.)*

We are studying a 31-year-old male with hypermethioninemia which we have documented as being due to a deficiency of the "high-K_m" hepatic isozyme of methionine adenosyltransferase.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00936-23 LGCB

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Homocystinuria: Methionine Metabolism in Mammals

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

S. H. Mudd Chief, Section on Alkaloid Biosynthesis LGCB NIMH

COOPERATING UNITS *(if any)*

William Gahl Human Genetics Branch Child Health and Human Development NIH

LAB/BRANCH

Laboratory of General and Comparative Biochemistry

SECTION

Section on Alkaloid Biosynthesis

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1/12	1/12	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.)*

We are studying a 31-year-old male with hypermethioninemia which we have documented as being due to a deficiency of the "high-K_m" hepatic isozyme of methionine adenosyltransferase.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00940-06 LGCB

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Methionine Biosynthesis in Higher Plants

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

A.H. Datko	Biologist	LGCB NIMH
S.H. Mudd	Chief, Section on Alkaloid Biosynthesis	LGCB NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of General and Comparative Biochemistry

SECTION

Section on Alkaloid Biosynthesis

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.7	1.7	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.)*

Various aspects of the biosynthetic pathways which culminate in phosphatidylcholine and phosphatidylethanolamine have been investigated in Lemna. Formation of ethanolamine occurs via decarboxylation of a water soluble compound (probably serine, although phosphoserine has not been completely eliminated as a candidate). Methylation occurs almost entirely ($\geq$ 99%) at the phosphobase level. These processes are stringently controlled by, respectively, ethanolamine and choline, which are taken up from the external medium via specific and avid active transport mechanisms.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00940-06 LGCB

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Methionine Biosynthesis in Higher Plants

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

A.H. Datko	Biologist	LGCB NIMH
S.H. Mudd	Chief, Section on Alkaloid Biosynthesis	LGCB NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of General and Comparative Biochemistry

SECTION

Section on Alkaloid Biosynthesis

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.7	1.7	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.)*

Various aspects of the biosynthetic pathways which culminate in phosphatidylcholine and phosphatidylethanolamine have been investigated in Lemna. Formation of ethanolamine occurs via decarboxylation of a water soluble compound (probably serine, although phosphoserine has not been completely eliminated as a candidate). Methylation occurs almost entirely ($\geq$ 99%) at the phosphobase level. These processes are stringently controlled by, respectively, ethanolamine and choline, which are taken up from the external medium via specific and avid active transport mechanisms.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00942-05 LGCB

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Biochemical Reactions in Mammalian Cell Chemotaxis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.	R. R. Aksamit	Research Chemist	LGCB NIMH
	P. S. Backlund, Jr.	Senior Staff Fellow	LGCB NIMH
	G. L. Cantoni	Chief, Laboratory of General and Comparative Biochemistry	LGCB NIMH

COOPERATING UNITS *(if any)*

Office of Biologics, FDA

LAB/BRANCH

Laboratory of General and Comparative Biochemistry

SECTION

Section on Proteins

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1	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.)*

Chemotaxis by the RAW264 mouse macrophage cell line was inhibited by 3-deazaadenosine but not by 3-deazaaristeromycin. A search for biochemical reactions inhibited by 3-deazaadenosine but not by 3-deazaaristeromycin has revealed that only one reaction, the synthesis of a small number of proteins identified after separation by two-dimensional polyacrylamide gel electrophoresis, has the necessary inhibitor specificity for involvement in the 3-deazaadenosine-sensitive step of chemotaxis. A study with several adenosine analogs showed a correlation between inhibition of chemotaxis and inhibition of the synthesis of a common subset of proteins. These analogs also inhibited the synthesis of polyadenylated mRNA, leading us to postulate that incubation of cells with 3-deazaadenosine inhibits a methylation reaction that is required for the formation of a functional mRNA coding for one or more proteins required for chemotaxis.

Experiments to identifiy attractant-specific proteins have been limited because chemically defined attractants for RAW264 cells have not been available. This problem has been overcome by the isolation of a stable cell hybrid from a fusion between human leukocytes and a thioguanine-resistant RAW264 cell line. The hybrid expressed functional genes for chemotaxis to fMet-leu-phe, a commercially available synthetic attractant. Binding of fMet-leu-phe to hybrid cell membranes indicated that the binding constant was 2 nM and each cell had an average of 1200 receptors.

In addition to chemotactic receptors, one or more guanine nucleotide binding proteins are required for chemotaxis by RAW264 and the hybrid cells. This conclusion is based on the observation that chemotaxis of either RAW264 or hybrid cells is inhibited upon incubation of the cells with either cholera toxin or pertussis toxin. In all cases entry of the toxin is required and there is a correlation between toxin-catalysed ADP-ribosylation of a guanine nucleotide binding protein and the inhibition of chemotaxis. Although both cholera toxin and pertussis toxin affect cAMP levels, elevated cAMP levels per se do not inhibit chemotaxis.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00942-05 LGCB

ERIOD COVERED

October 1, 1985 to September 30, 1986

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

Biochemical Reactions in Mammalian Cell Chemotaxis

RINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.	R. R. Aksamit	Research Chemist	LGCB NIMH
	P. S. Backlund, Jr.	Senior Staff Fellow	LGCB NIMH
	G. L. Cantoni	Chief, Laboratory of General and Comparative Biochemistry	LGCB NIMH

OOPERATING UNITS *(if any)*

Office of Biologics, FDA

AB/BRANCH

Laboratory of General and Comparative Biochemistry

ECTION

Section on Proteins

ISTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

OTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1	0.5	0.5

HECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 00943-05 LGCB

PERIOD COVERED: October 1, 1985 to September 30, 1986

TITLE OF PROJECT (*80 characters or less. Title must fit on one line between the borders.*)
Pathways of Methionine and Threonine Metabolism and Their Control in Higher Plants

PRINCIPAL INVESTIGATOR (*List other professional personnel below the Principal Investigator.*) (*Name, title, laboratory, and institute affiliation*)

J. Giovanelli	Research Chemist	LGCB NIMH
S.H. Mudd	Chief, Section on Alkaloid Biosynthesis	LGCB NIMH
A.H. Datko	Biologist	LGCB NIMH

COOPERATING UNITS (*if any*)

None

LAB/BRANCH
Laboratory of General and Comparative Biochemistry

SECTION
Section on Alkaloid Biosynthesis

INSTITUTE AND LOCATION
NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	1.2	0

CHECK APPROPRIATE BOX(ES)

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

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

Similar labeling patterns of threonine, isoleucine and methionine were obtained for metabolism of ^{14}C-aspartate and ^{14}C-homoserine in Lemna, arguing against channeling of aspartate into separate threonine and methionine branches. Labeling patterns obtained with these two isotopes in plants supplemented with threonine demonstrated little or no feedback regulation of threonine synthesis, in contrast to the marked feedback regulation by each of the other members of the aspartate family (methionine, isoleucine, lysine) on its own synthesis. This finding corroborates previous studies in which endogenous rates of threonine synthesis were determined by the extent of dilution of specific activity of ^{14}C-threonine fed exogenously, and agrees with our failure to establish any regulatory property of threonine synthase that would allow specific control of the threonine biosynthetic branch. Systematic studies on the growth effects of the 7 possible combinations of threonine, methionine and lysine, in conjuction with labeling patterns from ^{14}C-aspartate and ^{14}C-homoserine, revealed only one condition of "crossregulation", i.e. inhibition of methionine biosynthesis by supplementation with threonine plus lysine. Studies have recently been initiated on aspartokinase, which catalyzes the first step in the entry of aspartate into the aspartate family of amino acids. We developed a sensitive and specific assay for aspartokinase, which is currently being employed in examining the activities and properties of this enzyme from plants growing with a variety of amino acid supplements. Our research begins to reveal an unusual regulatory role of threonine whereby this amino acid regulates its own synthesis only under conditions of lysine overproduction and, in so doing, can deprive the plant of methionine. These findings, together with more recent tentative results, now allow us to propose a novel and logical strategy for the use of genetic engeneering in improving the nutritional quality of methionine and lysine in plants.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 00943-05 LGCB

PERIOD COVERED: October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Pathways of Methionine and Threonine Metabolism and Their Control in Higher Plants

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

J. Giovanelli	Research Chemist	LGCB NIMH
S.H. Mudd	Chief, Section on Alkaloid Biosynthesis	LGCB NIMH
A.H. Datko	Biologist	LGCB NIMH

COOPERATING UNITS *(if any)*: None

LAB/BRANCH: Laboratory of General and Comparative Biochemistry

SECTION: Section on Alkaloid Biosynthesis

INSTITUTE AND LOCATION: NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.2	1.2	0

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02321-01 LGCB

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

DNA Methylathion and Gene Differentiation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.	G. L. Cantoni	Chief, Laboratory of General and Comparative Biochemistry	LGCB
	A. Razin	Fogarty Scholar, The Hebrew University Jerusalem, Israel	
Others:	S. Agostini	Guest Researcher	LGCB
	T. Gomi	Visiting Fellow	LGCB

COOPERATING UNITS *(if any)*

Department of Cellular Biochemistry, The Hebrew University, Hadassah Medical School, Jerusalem, Israel 91010; Depaerment of Human Biopathology, University of Rome, La Sapienza, Rome, Italy

LAB/BRANCH

Laboratory of General and Comparative Biochemistry

SECTION

Section on Proteins

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.5	3	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.)*

When Friend Erytroleukemia cells (FELC) are exposed to a variety of chemical agents capable of inducing terminal differentiation their DNA undergoes a genome-wide demethylation in the absence of DNA replication. Considerable evidence has accumulated to indicate that demethylation of specific genes, or of portion of specific regions of the DNA, is correlated with gene expression. The transient genome-wide demethylation observed during FELC differentiation must be an expression of the fact that the overall pattern of DNA methylation changes during differentiation with some genes becoming active in transcription and others becoming silent. The mechanism of DNA demethylation is completely unknown: theoretically, inhibition during at least two cycles of DNA replication of maintenance methylase, an enzyme capable of methylating hemimethylated DNA, could result in DNA demethylation and changes in the DNA methylation pattern. However the inhibition of maintenance methylase can not be involved in the genome wide, transient demethylation that is observed in the early phases of FELC differentiation, since this occurs in the absence of DNA duplication.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02321-01 LGCB

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

DNA Methylathion and Gene Differentiation

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.	G. L. Cantoni	Chief, Laboratory of General and Comparative Biochemistry	LGCB
	A. Razin	Fogarty Scholar, The Hebrew University Jerusalem, Israel	
Others:	S. Agostini	Guest Researcher	LGCB
	T. Gomi	Visiting Fellow	LGCB

COOPERATING UNITS *(if any)*

Department of Cellular Biochemistry, The Hebrew University, Hadassah Medical School, Jerusalem, Israel 91010; Depaerment of Human Biopathology, University of Rome, La Sapienza, Rome, Italy

LAB/BRANCH

Laboratory of General and Comparative Biochemistry

SECTION

Section on Proteins

INSTITUTE AND LOCATION

NIMH, ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.5	3	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.)*

When Friend Erytroleukemia cells (FELC) are exposed to a variety of chemical agents capable of inducing terminal differentiation their DNA undergoes a genome-wide demethylation in the absence of DNA replication. Considerable evidence has accumulated to indicate that demethylation of specific genes, or of portion of specific regions of the DNA, is correlated with gene expression. The transient genome-wide demethylation observed during FELC differentiation must be an expression of the fact that the overall pattern of DNA methylation changes during differentiation with some genes becoming active in transcription and others becoming silent. The mechanism of DNA demethylation is completely unknown: theoretically, inhibition during at least two cycles of DNA replication of maintenance methylase, an enzyme capable of methylating hemimethylated DNA, could result in DNA demethylation and changes in the DNA methylation pattern. However the inhibition of maintenance methylase can not be involved in the genome wide, transient demethylation that is observed in the early phases of FELC differentiation, since this occurs in the absence of DNA duplication.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

ZO1 MH 00934-14 LMB

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

The Biochemical Basis of Peptide Receptor Activity

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	W. A. Klee	Chief, Sec. on Regulatory Proteins	LMB, NIMH
Others:	D. L. Newton	Guest Researcher	LMB, NIMH
	J.-Y. Ye	Guest Researcher	LMB, NIMH
	G. Milligan	Visiting Fellow	LMB, NIMH
	R. C. Rice	Research Chemist	LC, NIADDK
	A. E. Jacobson	Research Chemist	LC, NIADDK
	H. Higashida	Visiting Associate	LBG, NIHLB
	M. Nirenberg	Chief, Lab. Biochem. Genetics	LBG, NIHLB

COOPERATING UNITS *(if any)*

Laboratory of Neurophysiology, NINCDS; Laboratory of Chemistry, NIADDK; and Laboratory of Biochemical Genetics, NIHLB

LAB/BRANCH

Laboratory of Molecular Biology

SECTION

Section on Regulatory Proteins

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.0	3.0	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.)*

In the past year we have purified several of the components of the opiate receptor - adenylate cyclase system. Adenylate cyclase has been purified from rat brain and the GTP-binding regulatory proteins Gi and Gs were purified from rabbit liver. These purified proteins were reconstituted into liposomes from detergent solutions by dialysis in the presence of phospholipids. In the reconstituted vesicles adenylate cyclase activity is stimulated by Gs and the stimulated activity is inhibited by Gi or by the beta-gamma subunit complex of bovine transducin. Thus a completely defined system has been developed with which to study opiate receptor function.

We have also used specific antibodies which recognize the alpha subunits of Gi or of Go to quantitate these proteins in brain and other tissues and cells. These studies showed that brain membranes contain 1-2% of their total protein as Go, and allowed study of the ontogeny of the proteins in neo-natal rat brain. The antibodies also led to the discovery of a novel G protein which is the predominant pertussis-toxin substrate of C6 glioma cells. Studies aimed at clarifying the function of the several G proteins have been carried out with bradykinin and opiate receptor coupled processes in NG108-15 hybrid cells.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

ZO1 MH 00934-14 LMB

ERIOD COVERED

October 1, 1985 to September 30, 1986

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PI:	W. A. Klee	Chief, Sec. on Regulatory Proteins	LMB, NIMH
Others:	D. L. Newton	Guest Researcher	LMB, NIMH
	J.-Y. Ye	Guest Researcher	LMB, NIMH
	G. Milligan	Visiting Fellow	LMB, NIMH
	R. C. Rice	Research Chemist	LC, NIADDK
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	H. Higashida	Visiting Associate	LBG, NIHLB
	M. Nirenberg	Chief, Lab. Biochem. Genetics	LBG, NIHLB

OOPERATING UNITS *(if any)*

Laboratory of Neurophysiology, NINCDS; Laboratory of Chemistry, NIADDK; and Laboratory of Biochemical Genetics, NIHLB

AB/BRANCH

Laboratory of Molecular Biology

ECTION

Section on Regulatory Proteins

STITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

OTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.0	3.0	1.0

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

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: ZO1 MH 01035-18 LMB

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

The Process of Lysogeny

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	H. A. Nash	Chief, Sec. on Mole. Genetics	LMB, NIMH
Others:	P. Kitts	Visiting Associate	LMB, NIMH
	E. Richet	Visiting Associate	LMB, NIMH
	P. Abcarian	Guest Researcher	LMB, NIMH
	G. Zon	Chief, Lab. Mole. Pharma.	DBB, FDA
	J. Gardner	Associate Professor	Univ. of Illinois

COOPERATING UNITS *(if any)*

Division of Biochemistry & Biophysics, Center for Drugs & Biologics, FDA; Departments of Microbiology, University of Illinois, Urbana, IL

LAB/BRANCH

Laboratory of Molecular Biology

SECTION

Section on Molecular Genetics

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.6	2.6	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 biochemical pathway by which the DNA of bacteriophage lambda integrates into its E. coli host has been investigated. We analyzed features of attP, the DNA segment carried by the virus that is essential for integrative recombination. First, we determined the role within attP of three binding sites for an E. coli protein, IHF, by making oligonucleotide-directed mutations that inactivate each site. All three sites proved to be essential for efficient integration but subtle differences between the behavior of the mutants in vivo suggest different roles for the different sites. Second, we developed a method for studying the interaction of specific binding proteins with supertwisted DNA. We used this new DNA footprinting method to show that Int, a viral recombinase, and IHF cooperate to form a complex nucleoprotein structure at attP only when it is supercoiled. The degree and sign of supercoiling needed to generate the structure correlate well with those needed to promote integration. Finally, we used chemical and enzymatic DNA synthesis to construct analogs of the bacterial recombination site, attB, the contain phosphorothioates in place of critical phosphate residues in DNA. These analogs recombine poorly and accumulate Holliday structures, presumptive intermediates in recombination. We found that the formation of Holliday structures was independent of DNA homology between attB and attP but homology was essential to complete the recombination. This eliminates models that invoke homology for the synapsis step of recombination.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: ZO1 MH 01035-18 LMB

PERIOD COVERED

October 1, 1985 to September 30, 1986

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Others:	P. Kitts	Visiting Associate	LMB, NIMH
	E. Richet	Visiting Associate	LMB, NIMH
	P. Abcarian	Guest Researcher	LMB, NIMH
	G. Zon	Chief, Lab. Mole. Pharma.	DBB, FDA
	J. Gardner	Associate Professor	Univ. of Illinois

COOPERATING UNITS *(if any)*

Division of Biochemistry & Biophysics, Center for Drugs & Biologics, FDA; Departments of Microbiology, University of Illinois, Urbana, IL

LAB/BRANCH

Laboratory of Molecular Biology

SECTION

Section on Molecular Genetics

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.6	2.6	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.)*

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

ZO1 MH 02228-02 LMB

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Genetic Neurobiology of Drosophila

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	H. A. Nash	Chief, Sec. on Mole. Genetics	LMB, NIMH
Others:	S. R. Haynes	Guest Researcher	LMG, NICHD
	F. Forquignon	Guest Researcher	LMG, NICHD

COOPERATING UNITS *(if any)*

Laboratory of Molecular Genetics, NICHD

LAB/BRANCH

Laboratory of Molecular Biology

SECTION

Section on Molecular Genetics

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.25	0.25	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.)*

We have pursued our objective of applying pharamacological and genetic techniques to the neurobiology of Drosophila melanogaster. We explored protocols for chemical mutagenesis of adult male flies; improvements in these protocols are being tested. We have also examined the suitability of several pharamacologic compounds as selective agents in a hunt for mutants with altered synaptic transmission. The capacity of amitraz, an insecticide with octopamine agonist properties, to alter the behavior of Drosophila was demonstrated. However, the effect of amitraz was modest and could not be enhanced by exogenous octopamine. To study the affect of general anesthetics on Drosophila, we assembled an apparatus for the administration of reproducible concentrations of gas and volatile liquids to large numbers of flies. The dose-response curve for Halothane anesthesia of Drosophila was established and a search for mutants with altered susceptibility to this anesthetic is underway.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

ZO1 MH 02228-02 LMB

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

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PI:	H. A. Nash	Chief, Sec. on Mole. Genetics	LMB, NIMH
Others:	S. R. Haynes	Guest Researcher	LMG, NICHD
	F. Forquignon	Guest Researcher	LMG, NICHD

COOPERATING UNITS *(if any)*

Laboratory of Molecular Genetics, NICHD

LAB/BRANCH

Laboratory of Molecular Biology

SECTION

Section on Molecular Genetics

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.25	0.25	1.0

CHECK APPROPRIATE BOX(ES) —

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

☐ (a1) Minors

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

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

ZO1 MH 01037-18 LMB

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

The Role of the Cell Membrane in Cellular Organization: A Molecular Study

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D. M. Neville, Jr.	Chief, Sec. on Biophy. Chem.	LMB, NIMH
Others:	T. H. Hudson	Staff Fellow	LMB, NIMH
	J. W. Marsh	Staff Fellow	LMB, NIMH
	H. Wellhoener	Guest Researcher	LMB, NIMH
	D. A. Vallera	Assistant Professor	Univ. of Minnesota
	J. H. Kersey	Prof. of Pediatrics	Univ. of Minnesota

COOPERATING UNITS *(if any)*

Minnesota Bone Marrow Transplantation Group, University of Minnesota, Minneapolis, Minnesota

LAB/BRANCH

Laboratory of Molecular Biology

SECTION

Section of Biophysical Chemistry

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.5	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.)*

The general aim of this project is to determine the chemical interactions and energetics which are involved in the insertion of proteins into cellular membranes and/or the translocation of proteins across cellular membranes. The events are studied from the initial receptor binding to the final physiologic response or pathological response in the case of toxins such as ricin, colicins, diphtheria and tetanus toxins. Utilizing basic data from such studies immunotoxins (toxins linked to monoclonal antibodies) are constructed to serve as a new class of pharmacologic reagents to eliminate unwanted cell types such as cancer cells or T-4 lymphocytes in AIDS infections, or to manipulate specific cells such as T cell subsets to correct imbalences which exist in autoimmune diseases such as multiple sclerosis. In addition immunotoxins continue to prove useful in deminishing the incidence of graft-versus-host-disease following bone marrow transplantation and thus will also have utility in enzyme replacement therapy and organ transplantation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

ZO1 MH 01037-18 LMB

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

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PI:	D. M. Neville, Jr.	Chief, Sec. on Biophy. Chem.	LMB, NIMH
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	J. W. Marsh	Staff Fellow	LMB, NIMH
	H. Wellhoener	Guest Researcher	LMB, NIMH
	D. A. Vallera	Assistant Professor	Univ. of Minnesota
	J. H. Kersey	Prof. of Pediatrics	Univ. of Minnesota

COOPERATING UNITS *(if any)*

Minnesota Bone Marrow Transplantation Group, University of Minnesota, Minneapolis, Minnesota

LAB/BRANCH

Laboratory of Molecular Biology

SECTION

Section of Biophysical Chemistry

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.5	3.5	1.5

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

ZO1 MH 00934-14 LMB

RIOD COVERED

October 1, 1985 to September 30, 1986

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

The Biochemical Basis of Peptide Receptor Activity

INCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	W. A. Klee	Chief, Sec. on Regulatory Proteins	LMB, NIMH
Others:	D. L. Newton	Guest Researcher	LMB, NIMH
	J.-Y. Ye	Guest Researcher	LMB, NIMH
	G. Milligan	Visiting Fellow	LMB, NIMH
	R. C. Rice	Research Chemist	LC, NIADDK
	A. E. Jacobson	Research Chemist	LC, NIADDK
	H. Higashida	Visiting Associate	LBG, NIHLB
	M. Nirenberg	Chief, Lab. Biochem. Genetics	LBG, NIHLB

OPERATING UNITS *(if any)*

Laboratory of Neurophysiology, NINCDS; Laboratory of Chemistry, NIADDK; and Laboratory of Biochemical Genetics, NIHLB

B/BRANCH

Laboratory of Molecular Biology

CTION

Section on Regulatory Proteins

STITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.0	3.0	1.0

HECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

In the past year we have purified several of the components of the opiate receptor - adenylate cyclase system. Adenylate cyclase has been purified from rat brain and the GTP-binding regulatory proteins Gi and Gs were purified from rabbit liver. These purified proteins were reconstituted into liposomes from detergent solutions by dialysis in the presence of phospholipids. In the reconstituted vesicles adenylate cyclase activity is stimulated by Gs and the stimulated activity is inhibited by Gi or by the beta-gamma subunit complex of bovine transducin. Thus a completely defined system has been developed with which to study opiate receptor function.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

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October 1, 1985 to September 30, 1986

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	J.-Y. Ye	Guest Researcher	LMB, NIMH
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	A. E. Jacobson	Research Chemist	LC, NIADDK
	H. Higashida	Visiting Associate	LBG, NIHLB
	M. Nirenberg	Chief, Lab. Biochem. Genetics	LBG, NIHLB

COOPERATING UNITS *(if any)*

Laboratory of Neurophysiology, NINCDS; Laboratory of Chemistry, NIADDK; and Laboratory of Biochemical Genetics, NIHLB

LAB/BRANCH

Laboratory of Molecular Biology

SECTION

Section on Regulatory Proteins

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.0	3.0	1.0

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: ZO1 MH 01035-18 LMB

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

The Process of Lysogeny

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	H. A. Nash	Chief, Sec. on Mole. Genetics	LMB, NIMH
Others:	P. Kitts	Visiting Associate	LMB, NIMH
	E. Richet	Visiting Associate	LMB, NIMH
	P. Abcarian	Guest Researcher	LMB, NIMH
	G. Zon	Chief, Lab. Mole. Pharma.	DBB, FDA
	J. Gardner	Associate Professor	Univ. of Illinois

COOPERATING UNITS *(if any)*

Division of Biochemistry & Biophysics, Center for Drugs & Biologics, FDA; Departments of Microbiology, University of Illinois, Urbana, IL

LAB/BRANCH

Laboratory of Molecular Biology

SECTION

Section on Molecular Genetics

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.6	2.6	1.0

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☐ (a2) Interviews

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

The biochemical pathway by which the DNA of bacteriophage lambda integrates into its E. coli host has been investigated. We analyzed features of attP, the DNA segment carried by the virus that is essential for integrative recombination. First, we determined the role within attP of three binding sites for an E. coli protein, IHF, by making oligonucleotide-directed mutations that inactivate each site. All three sites proved to be essential for efficient integration but subtle differences between the behavior of the mutants in vivo suggest different roles for the different sites. Second, we developed a method for studying the interaction of specific binding proteins with supertwisted DNA. We used this new DNA footprinting method to show that Int, a viral recombinase, and IHF cooperate to form a complex nucleoprotein structure at attP only when it is supercoiled. The degree and sign of supercoiling needed to generate the structure correlate well with those needed to promote integration. Finally, we used chemical and enzymatic DNA synthesis to construct analogs of the bacterial recombination site, attB, the contain phosphorothioates in place of critical phosphate residues in DNA. These analogs recombine poorly and accumulate Holliday structures, presumptive intermediates in recombination. We found that the formation of Holliday structures was independent of DNA homology between attB and attP but homology was essential to complete the recombination. This eliminates models that invoke homology for the synapsis step of recombination.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

ZO1 MH 01035-18 LMB

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

The Process of Lysogeny

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	H. A. Nash	Chief, Sec. on Mole. Genetics	LMB, NIMH
Others:	P. Kitts	Visiting Associate	LMB, NIMH
	E. Richet	Visiting Associate	LMB, NIMH
	P. Abcarian	Guest Researcher	LMB, NIMH
	G. Zon	Chief, Lab. Mole. Pharma.	DBB, FDA
	J. Gardner	Associate Professor	Univ. of Illinois

COOPERATING UNITS *(if any)*

Division of Biochemistry & Biophysics, Center for Drugs & Biologics, FDA; Departments of Microbiology, University of Illinois, Urbana, IL

LAB/BRANCH

Laboratory of Molecular Biology

SECTION

Section on Molecular Genetics

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.6	2.6	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 biochemical pathway by which the DNA of bacteriophage lambda integrates into its E. coli host has been investigated. We analyzed features of attP, the DNA segment carried by the virus that is essential for integrative recombination. First, we determined the role within attP of three binding sites for an E. coli protein, IHF, by making oligonucleotide-directed mutations that inactivate each site. All three sites proved to be essential for efficient integration but subtle differences between the behavior of the mutants in vivo suggest different roles for the different sites. Second, we developed a method for studying the interaction of specific binding proteins with supertwisted DNA. We used this new DNA footprinting method to show that Int, a viral recombinase, and IHF cooperate to form a complex nucleoprotein structure at attP only when it is supercoiled. The degree and sign of supercoiling needed to generate the structure correlate well with those needed to promote integration. Finally, we used chemical and enzymatic DNA synthesis to construct analogs of the bacterial recombination site, attB, the contain phosphorothioates in place of critical phosphate residues in DNA. These analogs recombine poorly and accumulate Holliday structures, presumptive intermediates in recombination. We found that the formation of Holliday structures was independent of DNA homology between attB and attP but homology was essential to complete the recombination. This eliminates models that invoke homology for the synapsis step of recombination.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

ZO1 MH 02228-02 LMB

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Genetic Neurobiology of Drosophila

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.)* *(Name, title, laboratory, and institute affiliation)*

PI:	H. A. Nash	Chief, Sec. on Mole. Genetics	LMB, NIMH
Others:	S. R. Haynes	Guest Researcher	LMG, NICHD
	F. Forquignon	Guest Researcher	LMG, NICHD

COOPERATING UNITS *(if any)*

Laboratory of Molecular Genetics, NICHD

LAB/BRANCH

Laboratory of Molecular Biology

SECTION

Section on Molecular Genetics

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.25	0.25	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.)*

We have pursued our objective of applying pharamacological and genetic techniques to the neurobiology of Drosophila melanogaster. We explored protocols for chemical mutagenesis of adult male flies; improvements in these protocols are being tested. We have also examined the suitability of several pharamacologic compounds as selective agents in a hunt for mutants with altered synaptic transmission. The capacity of amitraz, an insecticide with octopamine agonist properties, to alter the behavior of Drosophila was demonstrated. However, the effect of amitraz was modest and could not be enhanced by exogenous octopamine. To study the affect of general anesthetics on Drosophila, we assembled an apparatus for the administration of reproducible concentrations of gas and volatile liquids to large numbers of flies. The dose-response curve for Halothane anesthesia of Drosophila was established and a search for mutants with altered susceptibility to this anesthetic is underway.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

ZO1 MH 02228-02 LMB

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Genetic Neurobiology of Drosophila

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	H. A. Nash	Chief, Sec. on Mole. Genetics	LMB, NIMH
Others:	S. R. Haynes	Guest Researcher	LMG, NICHD
	F. Forquignon	Guest Researcher	LMG, NICHD

COOPERATING UNITS *(if any)*

Laboratory of Molecular Genetics, NICHD

LAB/BRANCH

Laboratory of Molecular Biology

SECTION

Section on Molecular Genetics

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.25	0.25	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.)*

We have pursued our objective of applying pharamacological and genetic techniques to the neurobiology of Drosophila melanogaster. We explored protocols for chemical mutagenesis of adult male flies; improvements in these protocols are being tested. We have also examined the suitability of several pharamacologic compounds as selective agents in a hunt for mutants with altered synaptic transmission. The capacity of amitraz, an insecticide with octopamine agonist properties, to alter the behavior of Drosophila was demonstrated. However, the effect of amitraz was modest and could not be enhanced by exogenous octopamine. To study the affect of general anesthetics on Drosophila, we assembled an apparatus for the administration of reproducible concentrations of gas and volatile liquids to large numbers of flies. The dose-response curve for Halothane anesthesia of Drosophila was established and a search for mutants with altered susceptibility to this anesthetic is underway.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

ZO1 MH 01037-18 LMB

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

The Role of the Cell Membrane in Cellular Organization: A Molecular Study

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D. M. Neville, Jr.	Chief, Sec. on Biophy. Chem.	LMB, NIMH
Others:	T. H. Hudson	Staff Fellow	LMB, NIMH
	J. W. Marsh	Staff Fellow	LMB, NIMH
	H. Wellhoener	Guest Researcher	LMB, NIMH
	D. A. Vallera	Assistant Professor	Univ. of Minnesota
	J. H. Kersey	Prof. of Pediatrics	Univ. of Minnesota

COOPERATING UNITS *(if any)*

Minnesota Bone Marrow Transplantation Group, University of Minnesota, Minneapolis, Minnesota

LAB/BRANCH

Laboratory of Molecular Biology

SECTION

Section of Biophysical Chemistry

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.5	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.)*

The general aim of this project is to determine the chemical interactions and energetics which are involved in the insertion of proteins into cellular membranes and/or the translocation of proteins across cellular membranes. The events are studied from the initial receptor binding to the final physiologic response or pathological response in the case of toxins such as ricin, colicins, diphtheria and tetanus toxins. Utilizing basic data from such studies immunotoxins (toxins linked to monoclonal antibodies) are constructed to serve as a new class of pharmacologic reagents to eliminate unwanted cell types such as cancer cells or T-4 lymphocytes in AIDS infections, or to manipulate specific cells such as T cell subsets to correct imbalences which exist in autoimmune diseases such as multiple sclerosis. In addition immunotoxins continue to prove useful in deminishing the incidence of graft-versus-host-disease following bone marrow transplantation and thus will also have utility in enzyme replacement therapy and organ transplantation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

ZO1 MH 01037-18 LMB

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

The Role of the Cell Membrane in Cellular Organization: A Molecular Study

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	D. M. Neville, Jr.	Chief, Sec. on Biophy. Chem.	LMB, NIMH
Others:	T. H. Hudson	Staff Fellow	LMB, NIMH
	J. W. Marsh	Staff Fellow	LMB, NIMH
	H. Wellhoener	Guest Researcher	LMB, NIMH
	D. A. Vallera	Assistant Professor	Univ. of Minnesota
	J. H. Kersey	Prof. of Pediatrics	Univ. of Minnesota

COOPERATING UNITS *(if any)*

Minnesota Bone Marrow Transplantation Group, University of Minnesota, Minneapolis, Minnesota

LAB/BRANCH

Laboratory of Molecular Biology

SECTION

Section of Biophysical Chemistry

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.5	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.)*

The general aim of this project is to determine the chemical interactions and energetics which are involved in the insertion of proteins into cellular membranes and/or the translocation of proteins across cellular membranes. The events are studied from the initial receptor binding to the final physiologic response or pathological response in the case of toxins such as ricin, colicins, diphtheria and tetanus toxins. Utilizing basic data from such studies immunotoxins (toxins linked to monoclonal antibodies) are constructed to serve as a new class of pharmacologic reagents to eliminate unwanted cell types such as cancer cells or T-4 lymphocytes in AIDS infections, or to manipulate specific cells such as T cell subsets to correct imbalences which exist in autoimmune diseases such as multiple sclerosis. In addition immunotoxins continue to prove useful in deminishing the incidence of graft-versus-host-disease following bone marrow transplantation and thus will also have utility in enzyme replacement therapy and organ transplantation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 00981-21 LNP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Mechanical, Thermal and Optical Signs of Excitation in the Nervous System

PRINCIPAL INVESTIGATOR *(List other professionel personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Ichiji Tasaki	Chief, Unit of Neurobiology	LNP, NIMH
Others:	Nobuko Tasaki	Guest Worker	LNP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Unit on Neurobiology, Laboratory of Neurophysiology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

(1) Improvement of Thermal Detector. Several years ago, we devised a sensitive detector for measuring small temperature changes in nervous tissues associated with their enhanced physiological activities. During the last fiscal year, we have greatly improved the signal-to-noise ratio of our thermal detector. It is now possible to apply our detector to various nervous tissues in which heat production during activity has never been detected. (2) Analysis of Sensory Processes in Frog Retina by Taking Heat Production as an Index. Our analysis of physiological events in the dark-adapted frog retina by using our thermal detector was initiated in March of 1985. Taking advantage of the improvement of our thermal detector, heat production in the retina induced by brief light stimuli was analyzed in detail. The major portion of our findings is expected to be published in the August issue of Biophysical Journal. (3) New Findings Obtained by Application of Heat Measurement Technique to Frog Spinal Cord. Using isolated bullfrog spinal cord, we succeeded in detecting heat production by the nerve cells in the cord following stimulation of the sensory nerve fibers. The time-resolution and the sensitivity of our thermal detector was high enough to permit a detailed analysis of the source of this heat. Our study of the effects of various pharmacological agents on the process of heat production by the spinal cord is now in progress. (4) Measurement of Mechanical and Optical Changes. By using various techniques developed in this laboratory, small movements and changes in turbidity of various nervous tissues were examined in conjunction with thermal measurements.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00981-21 LNP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Mechanical, Thermal and Optical Signs of Excitation in the Nervous System

PRINCIPAL INVESTIGATOR *(List other professionel personnel below the Principal Investigetor.) (Neme, title, laboratory, and institute affiliation)*

PI:	Ichiji Tasaki	Chief, Unit of Neurobiology	LNP, NIMH
Others:	Nobuko Tasaki	Guest Worker	LNP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Unit on Neurobiology, Laboratory of Neurophysiology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

(1) Improvement of Thermal Detector. Several years ago, we devised a sensitive detector for measuring small temperature changes in nervous tissues associated with their enhanced physiological activities. During the last fiscal year, we have greatly improved the signal-to-noise ratio of our thermal detector. It is now possible to apply our detector to various nervous tissues in which heat production during activity has never been detected. (2) Analysis of Sensory Processes in Frog Retina by Taking Heat Production as an Index. Our analysis of physiological events in the dark-adapted frog retina by using our thermal detector was initiated in March of 1985. Taking advantage of the improvement of our thermal detector, heat production in the retina induced by brief light stimuli was analyzed in detail. The major portion of our findings is expected to be published in the August issue of Biophysical Journal. (3) New Findings Obtained by Application of Heat Measurement Technique to Frog Spinal Cord. Using isolated bullfrog spinal cord, we succeeded in detecting heat production by the nerve cells in the cord following stimulation of the sensory nerve fibers. The time-resolution and the sensitivity of our thermal detector was high enough to permit a detailed analysis of the source of this heat. Our study of the effects of various pharmacological agents on the process of heat production by the spinal cord is now in progress. (4) Measurement of Mechanical and Optical Changes. By using various techniques developed in this laboratory, small movements and changes in turbidity of various nervous tissues were examined in conjunction with thermal measurements.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01081-16 LNP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Cerebral Control of Voluntary Movement

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	S. Pullman	Medical Staff Fellow	LNP, NIMH
	R. Watts	Medical Staff Fellow	LNP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Neurophysiology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

This project was designed to explore mechanisms of information processing occurring within cortical columns in the somatic sensorimotor cortex and to determine how this relates to limb movement. Extracellular, single neuron recording techniques in awake, behaving monkeys were used to study neural mechanisms involved in the cerebral motor control. Neuronal responses to cerebellar stimulation, obtained via chronically implanted electrodes in the brachium conjunctivum, were recorded using microelectrodes in the primary motor cortex. Stimulation of the cerebellum was delivered during various phases of forelimb movement, which consisted of alternation between two horizontal levers controlled by light cues indicating to the monkey when to move. A computer program was developed to control the light cues given to the monkeys indicating when to move, and to deliver the cerebellar stimulation at specific times during the forelimb movement. Input-output relations of the cortical columns were then studied by investigating the effects cerebellar afferents to the cerebrum on neurons in the different cortical layers.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01081-16 LNP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Cerebral Control of Voluntary Movement

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	S. Pullman	Medical Staff Fellow	LNP, NIMH
	R. Watts	Medical Staff Fellow	LNP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Neurophysiology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

This project was designed to explore mechanisms of information processing occurring within cortical columns in the somatic sensorimotor cortex and to determine how this relates to limb movement. Extracellular, single neuron recording techniques in awake, behaving monkeys were used to study neural mechanisms involved in the cerebral motor control. Neuronal responses to cerebellar stimulation, obtained via chronically implanted electrodes in the brachium conjunctivum, were recorded using microelectrodes in the primary motor cortex. Stimulation of the cerebellum was delivered during various phases of forelimb movement, which consisted of alternation between two horizontal levers controlled by light cues indicating to the monkey when to move. A computer program was developed to control the light cues given to the monkeys indicating when to move, and to deliver the cerebellar stimulation at specific times during the forelimb movement. Input-output relations of the cortical columns were then studied by investigating the effects cerebellar afferents to the cerebrum on neurons in the different cortical layers.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01090-10 LNP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Studies of Central Nervous System Functional Anatomy

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Miles Herkenham	Research Psychologist	LNP, NIMH
Others:	Stafford McLean	Senior Staff Fellow	LNP, NIMH
	Linda S. Brady	Staff Fellow	LNP, NIMH
	Richard B. Rothman	Guest Worker	LP-DSMHR, NIMH
	Kenner C. Rice	Chemist	LC, NIADDKD

COOPERATING UNITS *(if any)*

Neuroscience Branch, Laboratory of Preclinical Pharmacology, SEH, NIMH

LAB/BRANCH

Laboratory of Neurophysiology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.2	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.)*

A sensitive method for light microscopic localization of brain receptors by in vitro autoradiography was developed previously in this laboratory. By this method we have mapped the locations of drug and neurotransmitter receptors in the brains of rats and other vertebrates, including primates. Radiolabeled ligand binding using subtype-selective assay conditions confirmed the existence of anatomically distinct mu, delta, and kappa opiate receptor subtypes. A similar strategy led to the visualization of separate tachykinin receptors marked by radiolabeled substance P and eledoisin. Immunohistochemistry is used to compare the distributions of putative neurotransmitters and their receptors. The relationship of these localization patterns with other markers of brain heterogeneity, provided by tract tracing and enzyme staining, allows hypotheses about functional circuitry in the central nervous system. Physiological activation of neurochemically defined systems may lead to receptor occupation or regulation, which can be revealed and localized by in vivo as well as in vitro autoradiographic techniques.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01090-10 LNP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Studies of Central Nervous System Functional Anatomy

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Miles Herkenham	Research Psychologist	LNP, NIMH
Others:	Stafford McLean	Senior Staff Fellow	LNP, NIMH
	Linda S. Brady	Staff Fellow	LNP, NIMH
	Richard B. Rothman	Guest Worker	LP-DSMHR, NIMH
	Kenner C. Rice	Chemist	LC, NIADDKD

COOPERATING UNITS *(if any)*

Neuroscience Branch, Laboratory of Preclinical Pharmacology, SEH, NIMH

LAB/BRANCH

Laboratory of Neurophysiology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.2	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.)*

A sensitive method for light microscopic localization of brain receptors by in vitro autoradiography was developed previously in this laboratory. By this method we have mapped the locations of drug and neurotransmitter receptors in the brains of rats and other vertebrates, including primates. Radiolabeled ligand binding using subtype-selective assay conditions confirmed the existence of anatomically distinct mu, delta, and kappa opiate receptor subtypes. A similar strategy led to the visualization of separate tachykinin receptors marked by radiolabeled substance P and eledoisin. Immunohistochemistry is used to compare the distributions of putative neurotransmitters and their receptors. The relationship of these localization patterns with other markers of brain heterogeneity, provided by tract tracing and enzyme staining, allows hypotheses about functional circuitry in the central nervous system. Physiological activation of neurochemically defined systems may lead to receptor occupation or regulation, which can be revealed and localized by in vivo as well as in vitro autoradiographic techniques.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01092-08 LNP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

The Frontal Lobe and the Cerebral Control of Behavior

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Steven P. Wise	Research Biologist	LNP, NIMH
Others:	Kiyoshi Kurata	Visiting Fellow	LNP, NIMH
	Melvyn P. Heyes	Visiting Fellow	LNP, NIMH
	Eilon Vaadia	Visiting Associate	LNP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Neurophysiology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

The primate frontal lobe consists of three main parts: the primary motor cortex (MI), the prefrontal cortex (PF), and the nonprimary motor cortex. Each of the broad parts can be further subdivided into functionally and anatomically specialized cortical fields. Previous work on this project has shown that the nonprimary motor cortex is composed of at least two fields: the supplementary motor cortex (SM) and the premotor cortex (PM). SM and PM were differentiated from MI on the basis of neuronal responses to peripheral inputs, thresholds for evoking movements with intracortical electrical stimulation, the properties of single neurons during the performance of an operantly conditioned motor task, cytoarchitecture, and connectivity. In our physiological work, we have concentrated on one of these fields, PM, and an analysis of its neuronal activity during a variety of visual guided motor tasks. Our results support the hypothesis that PM plays a role in the visually guided behavior, especially those guided by arbitrary sensory cues, and the preparation for voluntary movements. These studies have provided new insight into the process termed behavioral set, which may underlie the ability of animals to make advantageous preparations for future actions. As such it is relevant to the finding that, in humans, deficits in the ability to change and form "sets" may reflect frontal lobe dysfunction and may underlie profound mental disorders. As such, the concept of behavioral set may provide a heuristically useful probe of frontal lobe function and represents a higher brain function amenable to both quantitative and qualitative neurophysiological analysis. Future work will be directed toward a direct analysis of PF physiology and organization, especially the interaction of frontal cortex with the basal ganglia and the dopaminergic projection to both structures.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 01092-08 LNP

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
The Frontal Lobe and the Cerebral Control of Behavior

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Steven P. Wise	Research Biologist	LNP, NIMH
Others:	Kiyoshi Kurata	Visiting Fellow	LNP, NIMH
	Melvyn P. Heyes	Visiting Fellow	LNP, NIMH
	Eilon Vaadia	Visiting Associate	LNP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Neurophysiology

SECTION

INSTITUTE AND LOCATION
NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

The primate frontal lobe consists of three main parts: the primary motor cortex (MI), the prefrontal cortex (PF), and the nonprimary motor cortex. Each of the broad parts can be further subdivided into functionally and anatomically specialized cortical fields. Previous work on this project has shown that the nonprimary motor cortex is composed of at least two fields: the supplementary motor cortex (SM) and the premotor cortex (PM). SM and PM were differentiated from MI on the basis of neuronal responses to peripheral inputs, thresholds for evoking movements with intracortical electrical stimulation, the properties of single neurons during the performance of an operantly conditioned motor task, cytoarchitecture, and connectivity. In our physiological work, we have concentrated on one of these fields, PM, and an analysis of its neuronal activity during a variety of visual guided motor tasks. Our results support the hypothesis that PM plays a role in the visually guided behavior, especially those guided by arbitrary sensory cues, and the preparation for voluntary movements. These studies have provided new insight into the process termed behavioral set, which may underlie the ability of animals to make advantageous preparations for future actions. As such it is relevant to the finding that, in humans, deficits in the ability to change and form "sets" may reflect frontal lobe dysfunction and may underlie profound mental disorders. As such, the concept of behavioral set may provide a heuristically useful probe of frontal lobe function and represents a higher brain function amenable to both quantitative and qualitative neurophysiological analysis. Future work will be directed toward a direct analysis of PF physiology and organization, especially the interaction of frontal cortex with the basal ganglia and the dopaminergic projection to both structures.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01095-02 LNP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Neuroanatomical/Chemical Organization of the Basal Ganglia

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Charles R. Gerfen	Senior Staff Fellow	LNP, NIMH
Others:	Dana C. Hilt	Medical Staff Fellow	IR BG, NHLBI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Neurophysiology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

The organization of the basal ganglia was studied in terms of biochemically defined neural circuits. A general method for such analysis has been developed that combines immunohistochemical labeling of selected neurons with a plant lectin and localization of neurochemicals associated with their specific axonal projections. This procedure, applied concurrently with autoradiographic localization of opiate receptors, and fluorescent retrograde axonal labeling of neurons has revealed important aspects of the functional organization of the basal ganglia. The striatum is a mosaic of two neurochemically distinct compartments. One, the "patches", contain mu opiate receptors in dense concentration and the other, the "matrix", contains 28kD-calcium binding protein (CaBP) and somatostatin immunoreactivity. This patch-matrix organization reflects the existence of parallel input-output systems which connect the cerebral cortex through the striatum to the substantia nigra. The nigrostriatal system is also compartmentalized, and consists of a non-dopaminergic projection to the matrix and dual dopamine (DA) containing systems to both compartments. Some nigral DA neurons contain CaBP and project to the matrix while others do not express CaBP and, project to the patches. Developmental studies and chemical lesion experiments suggest that these two nigrostriatal dopaminergic systems may be differentially susceptible to degeneration.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01095-02 LNP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

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PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Charles R. Gerfen	Senior Staff Fellow	LNP, NIMH
Others:	Dana C. Hilt	Medical Staff Fellow	IR BG, NHLBI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Neurophysiology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

The organization of the basal ganglia was studied in terms of biochemically defined neural circuits. A general method for such analysis has been developed that combines immunohistochemical labeling of selected neurons with a plant lectin and localization of neurochemicals associated with their specific axonal projections. This procedure, applied concurrently with autoradiographic localization of opiate receptors, and fluorescent retrograde axonal labeling of neurons has revealed important aspects of the functional organization of the basal ganglia. The striatum is a mosaic of two neurochemically distinct compartments. One, the "patches", contain mu opiate receptors in dense concentration and the other, the "matrix", contains 28kD-calcium binding protein (CaBP) and somatostatin immunoreactivity. This patch-matrix organization reflects the existence of parallel input-output systems which connect the cerebral cortex through the striatum to the substantia nigra. The nigrostriatal system is also compartmentalized, and consists of a non-dopaminergic projection to the matrix and dual dopamine (DA) containing systems to both compartments. Some nigral DA neurons contain CaBP and project to the matrix while others do not express CaBP and project to the patches. Developmental studies and chemical lesion experiments suggest that these two nigrostriatal dopaminergic systems may be differentially susceptible to degeneration.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 01096-02 LNP

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Spatial Organization of the Primate Motor Cortex

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Andrew R. Mitz	Staff Fellow	LNP, NIMH
Others:	Steven P. Wise	Research Biologist	LNP, NIMH
	Moshe Godschalk	Visiting Associate	LNP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Neurophysiology

SECTION

INSTITUTE AND LOCATION
NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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 purpose of this project is to examine the movement-related organization of the primary motor cortex (MI) and two closely related motor areas, the supplementary motor area (SM) and the premotor area (PM). The model species that has been chosen for study is the rhesus monkey, because the motor areas have been best characterized in this species. In the first part of this project electrical stimulation, including a refinement to the technique of intracortical microstimulation, is being employed to examine the efferent topography of the three motor areas.

In the second part of the project, the relationship between single-unit discharge patterns and learned movements is being studied to determine whether activity in the three motor areas is best related to the location of a target in space or to the limb movements necessary to acquire the target during a visual tracking task. It is the goal of this part of the project to determine the relative preponderances of different physiologically-defined cell types in each motor area.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01096-02 LNP

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Spatial Organization of the Primate Motor Cortex

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Andrew R. Mitz	Staff Fellow	LNP, NIMH
Others:	Steven P. Wise	Research Biologist	LNP, NIMH
	Moshe Godschalk	Visiting Associate	LNP, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Neurophysiology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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 purpose of this project is to examine the movement-related organization of the primary motor cortex (MI) and two closely related motor areas, the supplementary motor area (SM) and the premotor area (PM). The model species that has been chosen for study is the rhesus monkey, because the motor areas have been best characterized in this species. In the first part of this project electrical stimulation, including a refinement to the technique of intracortical microstimulation, is being employed to examine the efferent topography of the three motor areas.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00424-11 LCB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Biologically Active Peptides in the Brain

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Michael J. Brownstein, Chief, Laboratory of Cell Biology, NIMH

(see attached)

COOPERATING UNITS *(if any)* U.Strasbourg;U.Alabama;UTMB Galveston;LDN,NICHHD;Bowling Green SU; NIAAA;USUHS;INSERM;DRS;U.Oregon;Genentech,Inc.;FDA;Mass.Gen.Hospital;LMG,NINCDS; Cold Spring Harbor; Semmelweis U.Med.School;LNP,NINCDS;U.College London;ET NINCDS; BPB,NIMH;JHU;NCI;CNRS;LNN,NICHHD;Yale;NHLBI

LAB/BRANCH

Laboratory of Cell Biology

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
10		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.)*

We have continued to study the distribution of peptide-containing cells in the central nervous system, the biosynthesis of biologically active peptides, and the factors that regulate peptide secretion. Our studies of a number of peptides have contributed to a better understanding of the cell biology of peptidergic neurons and of their role in the brain.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00424-11 LCB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Biologically Active Peptides in the Brain

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Michael J. Brownstein, Chief, Laboratory of Cell Biology, NIMH

(see attached)

COOPERATING UNITS *(if any)* U.Strasbourg;U.Alabama;UTMB Galveston;LDN,NICHHD;Bowling Green SU; NIAAA;USUHS;INSERM;DRS;U.Oregon;Genentech,Inc.;FDA;Mass.Gen.Hospital;LMG,NINCDS; Cold Spring Harbor; Semmelweis U.Med.School;LNP,NINCDS;U.College London;ET NINCDS; BPB,NIMH;JHU;NCI;CNRS;LNN,NICHHD;Yale;NHLBI

LAB/BRANCH

Laboratory of Cell Biology

SECTION

Office of the Chief

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
10		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.)*

We have continued to study the distribution of peptide-containing cells in the central nervous system, the biosynthesis of biologically active peptides, and the factors that regulate peptide secretion. Our studies of a number of peptides have contributed to a better understanding of the cell biology of peptidergic neurons and of their role in the brain.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02302-01 LCB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Biochemical Studies on Myelin Basic Protein

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	R.E. Martenson	Research Chemist	LCB, NIMH
Others:	G.E. Deibler	Chemist	LCM, NIMH
	M.L. Pedersen	Biologist	LCM, NIMH
	E.C. Alvord, Jr.	Professor, Univ. of Wash. Sch. of Med.	
	G. Mendz	Assoc. Prof., University of Sydney	

COOPERATING UNITS *(if any)*

Neuropathology Dept., University of Washington Sch. of Med., Seattle, Washington
Dept. of Biochemistry, University of Sydney, New South Wales, Australia

LAB/BRANCH

Laboratory of Cell Biology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	1.5	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.)*

We have pursued our studies on the conformation of myelin basic protein by nuclear magnetic resonance spectroscopy, immunological reactions, and dicyanohemin-binding. The first method has revealed a number of short- and medium- range interactions between amino acid side chains which indicate specific foldings, such as reverse turns, in certain amino acid sequences. The last methods have provided evidence that the polypeptide chain is folded so that several regions distant along the chain are brought into close proximity. These studies have led to the proposal of a twisted β-sheet structure involving about 20% of the protein's residues. In addition, we have localized a second region of the protein capable of inducing experimental autoimmune encephalomyelitis in rabbits.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02302-01 LCB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Biochemical Studies on Myelin Basic Protein

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PI:	R.E. Martenson	Research Chemist	LCB, NIMH
Others:	G.E. Deibler	Chemist	LCM, NIMH
	M.L. Pedersen	Biologist	LCM, NIMH
	E.C. Alvord, Jr.	Professor, Univ. of Wash. Sch. of Med.	
	G. Mendz	Assoc. Prof., University of Sydney	

COOPERATING UNITS *(if any)*

Neuropathology Dept., University of Washington Sch. of Med., Seattle, Washington
Dept. of Biochemistry, University of Sydney, New South Wales, Australia

LAB/BRANCH

Laboratory of Cell Biology

SECTION

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	1.5	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.)*

We have pursued our studies on the conformation of myelin basic protein by nuclear magnetic resonance spectroscopy, immunological reactions, and dicyanohemin-binding. The first method has revealed a number of short- and medium- range interactions between amino acid side chains which indicate specific foldings, such as reverse turns, in certain amino acid sequences. The last methods have provided evidence that the polypeptide chain is folded so that several regions distant along the chain are brought into close proximity. These studies have led to the proposal of a twisted ß-sheet structure involving about 20% of the protein's residues. In addition, we have localized a second region of the protein capable of inducing experimental autoimmune encephalomyelitis in rabbits.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 00422-15 LCB

PERIOD COVERED: October 1, 1985 through September 30, 1986

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

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	M. Zatz	Section Chief	SBP, LCB, NIMH
Others:	J. Moskal	Sr. Staff Fellow	LCB, NIMH
	J. Wallingford	Guest Researcher	LCB, NIMH

COOPERATING UNITS *(if any)*:

LAB/BRANCH: Laboratory of Cell Biology

SECTION: Section on Biochemical Pharmacology

INSTITUTE AND LOCATION: NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	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.)*

Circadian rhythms and environmental lighting regulate a number of endocrine and behavioral functions. Dispersed chick pineal cells remain rhythmic and responsive to light in culture. Light, membrane potential, norepinephrine, and cyclic AMP regulate melatonin rhythms in these cells. A newly discovered retinaldehyde binding protein, with novel properties for a vertebrate photopigment, may mediate the effects of light on these cells.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00422-15 LCB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Neuropharmacology of Circadian Rhythms

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	M. Zatz	Section Chief	SBP, LCB, NIMH
Others:	J. Moskal	Sr. Staff Fellow	LCB, NIMH
	J. Wallingford	Guest Researcher	LCB, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Cell Biology

SECTION

Section on Biochemical Pharmacology

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	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.)*

Circadian rhythms and environmental lighting regulate a number of endocrine and behavioral functions. Dispersed chick pineal cells remain rhythmic and responsive to light in culture. Light, membrane potential, norepinephrine, and cyclic AMP regulate melatonin rhythms in these cells. A newly discovered retinaldehyde binding protein, with novel properties for a vertebrate photopigment, may mediate the effects of light on these cells.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00429-07 LCB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Biochemistry of Membranes

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	M. Zatz	Section Chief	SBP, LCB, NIMH
Others:	P. J. O'Brien	Section Chief	SCB, LVR, NEI
	T. Reisine	Sr. Staff Fellow	LCB, NIMH
	L. C. Mahan	Pharmacology Research Associate (NIGMS)	LCB, NIMH

COOPERATING UNITS *(if any)*

LVR, NEI

LAB/BRANCH

Laboratory of Cell Biology

SECTION

Section on Biochemical Pharmacology

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

1a) Lithium and tumor-promoting phorbol esters stimulate ACTH secretion by anterior pituitary tumor cells. Phorbal esters, which activate protein kinase C, also induce the translocation of this enzyme from the cytosol to the membranes. Membrane kinase activity then falls, corresponding to the desensitization of the cells to further stimulation. Lithium also desensitizes the cells, but neither causes translocation itself nor affects phorbol-ester induced translocation of protein kinase C.

1b) Phorbol esters also mimic the effects of certain neurotransmitters on brain. Treatment of hippocampal slices with phorbol ester caused translocation of protein kinase C activity from cytosol to membranes. However, experiments with carbachol, norepinephrine, glutamate, KCl, and lithium failed to demonstrate a similar translocation.

2. The acylation of rhodopsin by long chain fatty acids from acylcoenzyme A has been demonstrated in vivo and in vitro. Evidence has been obtained that the bond may be a thioester and that the transfer to mature rhodopsin, though physiologic, may not be enzymatic. Acylation of rhodopsin is prototypical of a new class of posttranslational modification of membrane receptors.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00429-07 LCB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Biochemistry of Membranes

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	M. Zatz	Section Chief	SBP,	LCB, NIMH
Others:	P. J. O'Brien	Section Chief	SCB,	LVR, NEI
	T. Reisine	Sr. Staff Fellow		LCB, NIMH
	L. C. Mahan	Pharmacology Research Associate (NIGMS)		LCB, NIMH

COOPERATING UNITS *(if any)*

LVR, NEI

LAB/BRANCH

Laboratory of Cell Biology

SECTION

Section on Biochemical Pharmacology

INSTITUTE AND LOCATION

NIMH, ADAMHA, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00427-09 LCB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

On the Mechanism of Signal Transduction Through Receptors

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Fusao Hirata, Visiting Scientist, Laboratory of Cell Biology, NIMH

See Attached Sheet

COOPERATING UNITS *(if any)*

See Attached Sheet

LAB/BRANCH

Laboratory of Cell Biology

SECTION

INSTITUTE AND LOCATION

NIMH ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

Lipocortins are phospholipase inhibitory proteins, which we discovered and characterized as second messengers of glucocorticoids, hormones from the adrenal cortex. The induction of the synthesis of these proteins by glucocorticoids occurs even in physiological doses and purified lipocortins can mimic some actions of glucocorticoids such as anti-inflammatory actions, immunosuppression, anti-edema action and arrest of cellular growth. These actions are attributable to the regulation of hormone-or neurotransmitter-induced phospholipid metabolisms (phosphatidylcholine and polyphosphoinositide turnovers) by lipocortins. Since lipocortins phosphorylated by tyrosine kinases and serine/threonine kinases are inactive to inhibit phospholipases, phosphorylation-dephosphorylation appears to play an important role in such regulation. Tyrosine kinases are closely associated with growth factor receptors such as EGF and insulin receptors, whereas serine/threonine kinases including protein kinase C are involved in bradykinin, fMetLeuPhe and other receptors.

All these observations implicate that noxious stimuli such as stresses can cause immunosuppression by inducing the synthesis of lipocortins via hypercorticoidemia and that various receptor functions can be modulated by phosphorylation-dephosphorylation of lipocortins. Thus, glucocorticoids can exert their many actions in various tissues and organs, mediating through lipocortins.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00427-09 LCB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

On the Mechanism of Signal Transduction Through Receptors

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Fusao Hirata, Visiting Scientist, Laboratory of Cell Biology, NIMH

See Attached Sheet

COOPERATING UNITS *(if any)*

See Attached Sheet

LAB/BRANCH

Laboratory of Cell Biology

SECTION

INSTITUTE AND LOCATION

NIMH ADAMHA, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

Lipocortins are phospholipase inhibitory proteins, which we discovered and characterized as second messengers of glucocorticoids, hormones from the adrenal cortex. The induction of the synthesis of these proteins by glucocorticoids occurs even in physiological doses and purified lipocortins can mimic some actions of glucocorticoids such as anti-inflammatory actions, immunosuppression, anti-edema action and arrest of cellular growth. These actions are attributable to the regulation of hormone-or neurotransmitter-induced phospholipid metabolisms (phosphatidylcholine and polyphosphoinositide turnovers) by lipocortins. Since lipocortins phosphorylated by tyrosine kinases and serine/threonine kinases are inactive to inhibit phospholipases, phosphorylation-dephosphorylation appears to play an important role in such regulation. Tyrosine kinases are closely associated with growth factor receptors such as EGF and insulin receptors, whereas serine/threonine kinases including protein kinase C are involved in bradykinin, fMetLeuPhe and other receptors.

All these observations implicate that noxious stimuli such as stresses can cause immunosuppression by inducing the synthesis of lipocortins via hypercorticoidemia and that various receptor functions can be modulated by phosphorylation-dephosphorylation of lipocortins. Thus, glucocorticoids can exert their many actions in various tissues and organs, mediating through lipocortins.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00434-05 LCB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Molecular Mechanisms of Receptor-Mediated Signal Transduction

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Julius Axelrod, Guest Researcher, Unit on Pharmacology, LCB, NIMH

Alberto Luini, Visiting Associate, LCB, NIMH
Carole L. Jelsema, Research Biologist, LCB, NIMH
Ronald M. Burch, Pharmacology Research Associate, LCB, NIMH
Lawrence C. Mahan, Pharmacology Research Associate, LCB, NIMH

COOPERATING UNITS *(if any)*

See Attached Sheet

LAB/BRANCH

Laboratory of Cell Biology

SECTION

INSTITUTE AND LOCATION

NIMH ADAMHA Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.0	5.0	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.)*

Secretion of adrenocorticotropin (ACTH) by AtT-20 pituitary tumor cells is under multi-hormonal control. Somatostatin (SRIF) inhibited ACTH secretion stimulated by cAMP-dependent and -independent pathways. SRIF inhibition of both adenylate cyclase and Ca^{++} entry via voltage-dependent channels was mediated by GTP-regulatory (G) proteins. In addition, G proteins mediated SRIF inhibition of ACTH release by phorbol esters (activation of C kinase) and by mechanisms distal to both the activation of cAMP-dependent kinase and Ca^{++} entry. Radioligand binding studies revealed a single class of SRIF receptor whose affinity was regulated by Na^{+} and GTP. These data suggest that inhibitory G proteins mediate both SRIF action and receptor desensitization through multiple transduction mechanisms.

GTP-regulatory proteins, in particular transducin, were shown to mediate light-induced stimulation of phospholipase A_2 and C (PLA_2, PLC) in rod outer segments (ROS) of bovine retina. Studies using G protein-specific agents, cholera toxin and pertussis toxin, in both light and dark-adpated ROS suggested a dual role for G proteins in both activation and inhibition of PLA_2, and PLC. In retina from Xenopus laevis, both somatostatin and dopamine inhibited the circadian rise in N-acetyl transferase (NAT), the rate limiting enzyme in melatonin synthesis. These effects appear mediated by G proteins through the inhibition of adenylate cyclase. In addition a role for arachidonic acid (AA) or AA metabolites in the regulation of NAT activity was found.

Alpha$_1$-adrenergic activation of PLA_2 and PLC was studied in FRTL-5 rat thyroid cells. α_1-Agonists increase PGE_2 formation from AA which stimulates cell growth. Both AA and inositolphosphate release were stimulated by GTP analogues, but only AA release was inhibited by pertussis toxin. This suggests that α_1-receptors can couple to two distinct G proteins in these cells.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00434-05 LCB

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Molecular Mechanisms of Receptor-Mediated Signal Transduction

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Julius Axelrod, Guest Researcher, Unit on Pharmacology, LCB, NIMH

Alberto Luini, Visiting Associate, LCB, NIMH
Carole L. Jelsema, Research Biologist, LCB, NIMH
Ronald M. Burch, Pharmacology Research Associate, LCB, NIMH
Lawrence C. Mahan, Pharmacology Research Associate, LCB, NIMH

COOPERATING UNITS *(if any)*

See Attached Sheet

LAB/BRANCH

Laboratory of Cell Biology

SECTION

INSTITUTE AND LOCATION

NIMH ADAMHA Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.0	5.0	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.)*

Secretion of adrenocorticotropin (ACTH) by AtT-20 pituitary tumor cells is under multi-hormonal control. Somatostatin (SRIF) inhibited ACTH secretion stimulated by cAMP-dependent and -independent pathways. SRIF inhibition of both adenylate cyclase and Ca^{++} entry via voltage-dependent channels was mediated by GTP-regulatory (G) proteins. In addition, G proteins mediated SRIF inhibition of ACTH release by phorbol esters (activation of C kinase) and by mechanisms distal to both the activation of cAMP-dependent kinase and Ca^{++} entry. Radioligand binding studies revealed a single class of SRIF receptor whose affinity was regulated by Na^{+} and GTP. These data suggest that inhibitory G proteins mediate both SRIF action and receptor desensitization through multiple transduction mechanisms.

GTP-regulatory proteins, in particular transducin, were shown to mediate light-induced stimulation of phospholipase A_2 and C (PLA_2, PLC) in rod outer segments (ROS) of bovine retina. Studies using G protein-specific agents, cholera toxin and pertussis toxin, in both light and dark-adpated ROS suggested a dual role for G proteins in both activation and inhibition of PLA_2 and PLC. In retina from Xenopus laevis, both somatostatin and dopamine inhibited the circadian rise in N-acetyl transferase (NAT), the rate limiting enzyme in melatonin synthesis. These effects appear mediated by G proteins through the inhibition of adenylate cyclase. In addition a role for arachidonic acid (AA) or AA metabolites in the regulation of NAT activity was found.

Alpha$_1$-adrenergic activation of PLA_2 and PLC was studied in FRTL-5 rat thyroid cells. α_1-Agonists increase PGE_2 formation from AA which stimulates cell growth. Both AA and inositolphosphate release were stimulated by GTP analogues, but only AA release was inhibited by pertussis toxin. This suggests that α_1-receptors can couple to two distinct G proteins in these cells.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01031-18 LNC

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

The Conversion of Phenylalanine to Tyrosine

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI	Seymour Kaufman	Chief	LNC NIMH
	Jennifer Tipper	Senior Staff Fellow	LNC NIMH
	John Donlon	Guest Researcher	LNC NIMH
	Michael Davis	Senior Staff Fellow	LNC NIMH
	Yohsuki Minatagowa	Visiting Scientist	LNC NIMH
	Desirazu Narasimha Rao	Visiting Fellow	LNC NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Neurochemistry

SECTION

INSTITUTE AND LOCATION

ADAMHA, NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.3	3.8	0.5

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

Limited proteolytic digestion of rat liver phenylalanine hydroxylase indicates that the molecule is composed of two separate domains.

Rat liver and kidney phenylalanine hydroxylase are differentially regulated by hormones.

Activity of rat liver phenylalanine hydroxylase can be doubled by increasing the dietary intake of iron.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01031-18 LNC

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

The Conversion of Phenylalanine to Tyrosine

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI	Seymour Kaufman	Chief	LNC NIMH
	Jennifer Tipper	Senior Staff Fellow	LNC NIMH
	John Donlon	Guest Researcher	LNC NIMH
	Michael Davis	Senior Staff Fellow	LNC NIMH
	Yohsuki Minatagowa	Visiting Scientist	LNC NIMH
	Desirazu Narasimha Rao	Visiting Fellow	LNC NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Neurochemistry

SECTION

INSTITUTE AND LOCATION

ADAMHA, NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.3	3.8	0.5

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

Limited proteolytic digestion of rat liver phenylalanine hydroxylase indicates that the molecule is composed of two separate domains.

Rat liver and kidney phenylalanine hydroxylase are differentially regulated by hormones.

Activity of rat liver phenylalanine hydroxylase can be doubled by increasing the dietary intake of iron.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01032-18 LNC

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Biosynthesis of Catecholamines

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI	Seymour Kaufman	Chief	LNC NIMH
	Thomas Nelson	Staff Fellow	LNC NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Neurochemistry

SECTION

INSTITUTE AND LOCATION

ADAMHA, NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

Tyrosine hydroxylase catalyzes the rate-limiting step in the biosynthesis of the neurotransmitters dopamine and norepinephrine. We have purified the enzyme from rat brain and are currently sequencing the peptide corresponding to the site phosphorylated by cAMP-dependent protein kinase.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01032-18 LNC

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Biosynthesis of Catecholamines

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI	Seymour Kaufman	Chief	LNC NIMH
	Thomas Nelson	Staff Fellow	LNC NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Neurochemistry

SECTION

INSTITUTE AND LOCATION

ADAMHA, NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

Tyrosine hydroxylase catalyzes the rate-limiting step in the biosynthesis of the neurotransmitters dopamine and norepinephrine. We have purified the enzyme from rat brain and are currently sequencing the peptide corresponding to the site phosphorylated by cAMP-dependent protein kinase.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01038-18 LNC

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Phenylketonuria and Other Diseases Caused by Defects in Biopterin-Dependent Enzymes

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI	Seymour Kaufman	Chief	LNC NIMH
	Sheldon Milstien	Research Chemist	LNC NIMH
	Harvey L. Levy	Professor	Harvard Med. Sch.

COOPERATING UNITS *(if any)*

Department of Pediatrics
Harvard Medical School
Boston, Massachusetts 02115

LAB/BRANCH

Laboratory of Neurochemistry

SECTION

INSTITUTE AND LOCATION

ADAMHA, NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
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.)*

Successful treatment of hyperphenylalaninemia due to a lack of dihydropteridine reductase must include supplementation with a tetrahydrofolate derivative.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01038-18 LNC

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Phenylketonuria and Other Diseases Caused by Defects in Biopterin-Dependent Enzymes

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI	Seymour Kaufman	Chief	LNC NIMH
	Sheldon Milstien	Research Chemist	LNC NIMH
	Harvey L. Levy	Professor	Harvard Med. Sch.

COOPERATING UNITS *(if any)*

Department of Pediatrics
Harvard Medical School
Boston, Massachusetts 02115

LAB/BRANCH

Laboratory of Neurochemistry

SECTION

INSTITUTE AND LOCATION

ADAMHA, NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
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.)*

Successful treatment of hyperphenylalaninemia due to a lack of dihydropteridine reductase must include supplementation with a tetrahydrofolate derivative.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01039-18 LNC

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Pteridine Biosynthesis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI	Sheldon Milstien	Research Chemist	LNC NIMH
	Seymour Kaufman	Chief	LNC NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Neurochemistry

SECTION

INSTITUTE AND LOCATION

ADAMHA, NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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 biosynthesis of tetrahydrobiopterin (BH_4 had previously been shown to proceed through tetrahydro intermediates. A new reductase has now been purified from rat brain which catalyzes the formation of one of the postulated intermediates. The role of this intermediate has now been clarified.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01039-18 LNC

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Pteridine Biosynthesis

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI	Sheldon Milstien	Research Chemist	LNC NIMH
	Seymour Kaufman	Chief	LNC NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Neurochemistry

SECTION

INSTITUTE AND LOCATION

ADAMHA, NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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 biosynthesis of tetrahydrobiopterin (BH_4 had previously been shown to proceed through tetrahydro intermediates. A new reductase has now been purified from rat brain which catalyzes the formation of one of the postulated intermediates. The role of this intermediate has now been clarified.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 01040-02 LNC

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

The Conversion of Phenylalanine to Tyrosine

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI	Seymour Kaufman	Chief	LNC NIMH
	Sheldon Milstien	Research Chemist	LNC NIMH
	Bruce Citron	Senior Staff Fellow	LNC NIMH
	Y. C. Liu	Visiting Fellow	LNC NIMH
	D.N. Rao	Visiting Fellow	LNC NIMH
	Savio L.C. Woo	Professor	Baylor Univ.
	Fred. D. Ledley	Research Associate	Baylor Univ.

COOPERATING UNITS *(if any)*

Department of Cell Biology
Baylor College of Medicine, Texas Medical Center
Houston, Texas 77030

LAB/BRANCH

Laboratory of Neurochemistry

SECTION

INSTITUTE AND LOCATION

ADAMHA, NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.9	2.4	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.)*

Successful treatment of hyperphenylalaninemia due to a lack of dihydropteridine reductase must include supplementation with a tetrahydrofolate derivative.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 01040-02 LNC

PERIOD COVERED: October 1, 1985 through September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: The Conversion of Phenylalanine to Tyrosine

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI	Seymour Kaufman	Chief	LNC NIMH
	Sheldon Milstien	Research Chemist	LNC NIMH
	Bruce Citron	Senior Staff Fellow	LNC NIMH
	Y. C. Liu	Visiting Fellow	LNC NIMH
	D.N. Rao	Visiting Fellow	LNC NIMH
	Savio L.C. Woo	Professor	Baylor Univ.
	Fred. D. Ledley	Research Associate	Baylor Univ.

COOPERATING UNITS *(if any)*

Department of Cell Biology
Baylor College of Medicine, Texas Medical Center
Houston, Texas 77030

LAB/BRANCH: Laboratory of Neurochemistry

SECTION:

INSTITUTE AND LOCATION: ADAMHA, NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.9	2.4	0.5

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.)*

Successful treatment of hyperphenylalaninemia due to a lack of dihydropteridine reductase must include supplementation with a tetrahydrofolate derivative.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00881-30 LCM

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Intermediary Energy Metabolism in Mammalian Brain

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Elaine E. Kaufman	Research Chemist	LCM, NIMH
Others:	Thomas Nelson	Senior Staff Fellow	LCM, NIMH
	Louis Sokoloff	Chief	LCM, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Developmental Neurochemistry Section

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.75	2.25	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 project described in this report has involved two general areas: 1) the identification of and regulatory mechanisms involved in the biosynthetic and degradative pathways for γ-hydroxybutyrate (GHB), a naturally occurring compound in mammalian brain which is thought to function either as a neuromodulator or as a neurotransmitter, and 2) the study of certain pharmacological effects of GHB especially those effects which bear a close resemblance to those of opiates such as morphine.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00881-30 LCM

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Intermediary Energy Metabolism in Mammalian Brain

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Elaine E. Kaufman	Research Chemist	LCM, NIMH
Others:	Thomas Nelson	Senior Staff Fellow	LCM, NIMH
	Louis Sokoloff	Chief	LCM, NIMH

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Developmental Neurochemistry Section

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.75	2.25	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 project described in this report has involved two general areas: 1) the identification of and regulatory mechanisms involved in the biosynthetic and degradative pathways for γ-hydroxybutyrate (GHB), a naturally occurring compound in mammalian brain which is thought to function either as a neuromodulator or as a neurotransmitter, and 2) the study of certain pharmacological effects of GHB especially those effects which bear a close resemblance to those of opiates such as morphine.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00882-19 LCM

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Studies on Regional Cerebral Circulation and Metabolism

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	Louis Sokoloff	Chief, Lab. Cerebral Metabolism	LCM, NIMH
Others:	Charles Kennedy	Guest Researcher	LCM, NIMH
	Thomas Nelson	Medical Officer	LCM, NIMH
	Carolyn B. Smith	Research Chemist	LCM, NIMH
	Gerald A. Dienel	Staff Fellow	LCM, NIMH
	Nancy Cruz	Biologist	LCM, NIMH

COOPERATING UNITS *(if any)*

Theoretical Statistics & Mathematics Branch, NIMH; NINCDS, NIH; NIDA, ARC, Baltimore, Maryland.

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Developmental Neurochemistry Section

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
9.50	6.00	3.50

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 method has been developed for the quantitative determination of the rates of local glucose consumption in the discrete functional and structural components of the brain in conscious or anesthetized laboratory animals. The method is based on the use of [^{14}C]deoxyglucose as a tracer for glucose flux through the hexokinase step. Local [^{14}C]deoxyglucose-6-phosphate concentrations in the tissues of the CNS are measured by a quantitative autoradiographic method. Inasmuch as the autoradiographs of the relative rates of local glucose consumption can be used directly for metabolic mapping of functionally linked structures in the CNS, the method is being used to study alterations in the energy metabolism of the discrete functional and structural components of the brain in a variety of physiological, pharmacological, and pathological states.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 00882-19 LCM

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Studies on Regional Cerebral Circulation and Metabolism

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	Louis Sokoloff	Chief, Lab. Cerebral Metabolism	LCM, NIMH
Others:	Charles Kennedy	Guest Researcher	LCM, NIMH
	Thomas Nelson	Medical Officer	LCM, NIMH
	Carolyn B. Smith	Research Chemist	LCM, NIMH
	Gerald A. Dienel	Staff Fellow	LCM, NIMH
	Nancy Cruz	Biologist	LCM, NIMH

COOPERATING UNITS *(if any)*

Theoretical Statistics & Mathematics Branch, NIMH; NINCDS, NIH; NIDA, ARC, Baltimore, Maryland.

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Developmental Neurochemistry Section

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
9.50	6.00	3.50

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 method has been developed for the quantitative determination of the rates of local glucose consumption in the discrete functional and structural components of the brain in conscious or anesthetized laboratory animals. The method is based on the use of [^{14}C]deoxyglucose as a tracer for glucose flux through the hexokinase step. Local [^{14}C]deoxyglucose-6-phosphate concentrations in the tissues of the CNS are measured by a quantitative autoradiographic method. Inasmuch as the autoradiographs of the relative rates of local glucose consumption can be used directly for metabolic mapping of functionally linked structures in the CNS, the method is being used to study alterations in the energy metabolism of the discrete functional and structural components of the brain in a variety of physiological, pharmacological, and pathological states.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00887-09 LCM

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

The Extended Visual System of the Macaque Monkey

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	Charles Kennedy	Guest Researcher	LCM, NIMH
Other:	Louis Sokoloff	Chief	LCM, NIMH
	Mortimer Mishkin	Chief	LN, NIMH
	Jocelyn Bechevalier	Visiting Associate	LN, NIMH

COOPERATING UNITS *(if any)*

Laboratory of Neuropsychology, NIMH

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Developmental Neurochemistry Section

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	1.25	0.75

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 localize the parts of brain which participate in processing visual information, we have measured rates of local cerebral glucose utilization in monkeys during the performance of a task cued by specific visual stimuli. A surgical preparation resulting in one hemisphere's being totally deprived of visual input while the other is normally sensitive to the visual cues has permitted the mapping of those cortical areas beyond the primary visual cortex which are involved in processing visual information. We now wish to learn of the functional development of this extended cortical pathway and so are continuing these same studies in the monkey at various postnatal ages. Although the project began with its focus on mapping the visually responsive cortical areas, the experiments also permit an analysis of the sensory-motor system. Normal control monkeys with their visual pathways intact responded to the visual cues by pressing a lever with one hand. This invoked an asymmetrical pattern of local glucose utilization in brain involving a wide expanse of cortical and sub-cortical structures. An analysis of the pattern of asymmetry provides new information with respect to the localization sensory-motor function. The data obtained to date indicate that a much larger portion of brain regions are unilaterally activated on unimanual activity than has been appreciated previously.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00887-09 LCM

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

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PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	Charles Kennedy	Guest Researcher	LCM, NIMH
Other:	Louis Sokoloff	Chief	LCM, NIMH
	Mortimer Mishkin	Chief	LN, NIMH
	Jocelyn Bechevalier	Visiting Associate	LN, NIMH

COOPERATING UNITS *(if any)*

Laboratory of Neuropsychology, NIMH

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Developmental Neurochemistry Section

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.0	1.25	0.75

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 localize the parts of brain which participate in processing visual information, we have measured rates of local cerebral glucose utilization in monkeys during the performance of a task cued by specific visual stimuli. A surgical preparation resulting in one hemisphere's being totally deprived of visual input while the other is normally sensitive to the visual cues has permitted the mapping of those cortical areas beyond the primary visual cortex which are involved in processing visual information. We now wish to learn of the functional development of this extended cortical pathway and so are continuing these same studies in the monkey at various postnatal ages. Although the project began with its focus on mapping the visually responsive cortical areas, the experiments also permit an analysis of the sensory-motor system. Normal control monkeys with their visual pathways intact responded to the visual cues by pressing a lever with one hand. This invoked an asymmetrical pattern of local glucose utilization in brain involving a wide expanse of cortical and sub-cortical structures. An analysis of the pattern of asymmetry provides new information with respect to the localization sensory-motor function. The data obtained to date indicate that a much larger portion of brain regions are unilaterally activated on unimanual activity than has been appreciated previously.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00889-07 LCM

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

A Method for the Determination of Local Rates of Protein Synthesis in Brain

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	Carolyn B. Smith	Chemist	LCM, NIMH
Others:	Louis Sokoloff	Chief	LCM, NIMH
	Kathleen Schmidt	Computer Systems Analyst	LCM, NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Developmental Neurochemistry Section

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.9	0.7	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.)*

A method is being developed for the estimation of local rates of protein synthesis in brain in vivo. The method is based on the use of L-[1-^{14}C]leucine as a tracer for the incorporation of leucine into protein. Six kinetic models for the behavior of leucine on brain have been designed. By mathematical analysis of the kinetics of exchange of the amino acid between plasma and the tissue pool(s) and its incorporation into protein, equations have been derived for each model that define the rate of amino acid incorporation into protein in terms of the time course of plasma specific activity, final tissue concentration of ^{14}C, and experimentally determined kinetic constants. Tissue concentrations of ^{14}C are determined by quantitative autoradiography. Experiments are being carried out to test the validity of the various models and to determine the kinetic constants to be used in the operational equation.

In order to examine the potential usefulness of the methods, studies of neurobiological problems are being pursued with the assumption that there is no admixture of leucine derived from protein degradation with the precursor pool. These studies include the effects of aging, development, hypothyroidism, regeneration and sleep on local rates of cerebral protein synthesis.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00889-07 LCM

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

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P.I.:	Carolyn B. Smith	Chemist	LCM, NIMH
Others:	Louis Sokoloff	Chief	LCM, NIMH
	Kathleen Schmidt	Computer Systems Analyst	LCM, NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Developmental Neurochemistry Section

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.9	0.7	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.)*

A method is being developed for the estimation of local rates of protein synthesis in brain in vivo. The method is based on the use of L-[1-^{14}C]leucine as a tracer for the incorporation of leucine into protein. Six kinetic models for the behavior of leucine on brain have been designed. By mathematical analysis of the kinetics of exchange of the amino acid between plasma and the tissue pool(s) and its incorporation into protein, equations have been derived for each model that define the rate of amino acid incorporation into protein in terms of the time course of plasma specific activity, final tissue concentration of ^{14}C, and experimentally determined kinetic constants. Tissue concentrations of ^{14}C are determined by quantitative autoradiography. Experiments are being carried out to test the validity of the various models and to determine the kinetic constants to be used in the operational equation.

In order to examine the potential usefulness of the methods, studies of neurobiological problems are being pursued with the assumption that there is no admixture of leucine derived from protein degradation with the precursor pool. These studies include the effects of aging, development, hypothyroidism, regeneration and sleep on local rates of cerebral protein synthesis.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00900-29 LCM

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Biochemical Studies on Myelin and Myelin Basic Protein

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	R. E. Martenson	Research Chemist	LCM, NIMH
Others:	G. E. Deibler	Research Chemist	LCM, NIMH
	M. L. Pedersen	Biologist	LCM, NIMH
	A. Stone	Research Chemist	LCB, NIMH
	E. C. Alvord, Jr.	Professor, Univ. of Wash. Sch. of Med.	
	G. Mendz	Assoc. Prof., University of Sydney	
	N. Sternberger	Assoc. Prof., University of Rochester	

COOPERATING UNITS *(if any)*

Neuropathology Dept., University of Washington Sch. of Med., Seattle, Washington
School of Chemistry, University of Sydney, New South Wales, Australia
Center for Brain Research, University of Rochester, Rochester, New York

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER

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 transferred to Project No. Z01 MH 02302-01, Laboratory of Cell Biology, NIMH as the result of the Principal Investigator's transfer to that laboratory on September 1, 1985.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00900-29 LCM

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Biochemical Studies on Myelin and Myelin Basic Protein

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	R. E. Martenson	Research Chemist	LCM, NIMH
Others:	G. E. Deibler	Research Chemist	LCM, NIMH
	M. L. Pedersen	Biologist	LCM, NIMH
	A. Stone	Research Chemist	LCB, NIMH
	E. C. Alvord, Jr.	Professor, Univ. of Wash. Sch. of Med.	
	G. Mendz	Assoc. Prof., University of Sydney	
	N. Sternberger	Assoc. Prof., University of Rochester	

COOPERATING UNITS *(if any)*

Neuropathology Dept., University of Washington Sch. of Med., Seattle, Washington
School of Chemistry, University of Sydney, New South Wales, Australia
Center for Brain Research, University of Rochester, Rochester, New York

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

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 transferred to Project No. Z01 MH 02302-01, Laboratory of Cell Biology, NIMH as the result of the Principal Investigator's transfer to that laboratory on September 1, 1985.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00901-30 LCM

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Immunologic Reactivity of Myelin Basic Protein

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	M. W. Kies	Chemist	LCM, NIMH
Others:	B. F. Driscoll	Research Biologist	LCM, NIMH
	J. Kira	Visiting Fellow	LCM, NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Section on Developmental Neurochemistry

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

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 as the result of reorganization within the Laboratory.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00901-30 LCM

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Immunologic Reactivity of Myelin Basic Protein

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	M. W. Kies	Chemist	LCM, NIMH
Others:	B. F. Driscoll	Research Biologist	LCM, NIMH
	J. Kira	Visiting Fellow	LCM, NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Section on Developmental Neurochemistry

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

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 as the result of reorganization within the Laboratory.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00902-20 LCM

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Induction and Prevention of Experimental Allergic Encephalomyelitis (EAE)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	B. F. Driscoll	Research Biologist	LCM, NIMH
Others:	M. W. Kies	Chemist	LCM, NIMH
	E. C. Alvord, Jr.	Professor, Univ. of Wash.	School of Med.

COOPERATING UNITS *(if any)*

Neuropathology Department, University of Washington School of Medicine, Seattle, Washington

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Section on Developmental Neurochemistry

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

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 as the result of reorganization within the Laboratory.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00902-20 LCM

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Induction and Prevention of Experimental Allergic Encephalomyelitis (EAE)

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	B. F. Driscoll	Research Biologist	LCM, NIMH
Others:	M. W. Kies	Chemist	LCM, NIMH
	E. C. Alvord, Jr.	Professor, Univ. of Wash.	School of Med.

COOPERATING UNITS *(if any)*

Neuropathology Department, University of Washington School of Medicine, Seattle, Washington

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Section on Developmental Neurochemistry

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:

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 as the result of reorganization within the Laboratory.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00903-09 LCM

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Purification and Identification of Brain Proteinases and their Cleavage Products

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	Gladys E. Deibler	Chemist	LCM, NIMH
Other:	Marian W. Kies	Chemist	LCM, NIMH

COOPERATING UNITS *(if any)*

Lab. Cell Biology, NIMH; Lab. Experimental Carcinogenesis, NCI;
Lab. Molecular Genetics, NINCDS

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Section on Developmental Neurochemistry

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	1.5	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.)*

Our investigation of human myelin basic protein (HBP) extracted from whole rain has led to the isolation and identification of a new form of HBP with a olecular weight of 17.2 kDa. The more common form is an 18.5 kDa protein. The ew form of HBP was successfully separated from HBP-component 3 by a newly developed rocedure on FPLC (Fast Protein Liquid Chromotography). Based on recoveries from ach step of the procedure we estimated that the new form constituted about 13% of he total HBP. In collaboration with Dr. Henry Krutzsch, NCI, we have shown that oth the 17.2 and the 18.5 kDa proteins have blocked amino termini and identical arboxyl termini. When the HPLC elution patterns of the two proteins were compared, e found that four peaks in the chromatogram of the larger protein were missing rom the chromatogram of the 17.2 kDa protein. In addition an extra peak was found n the elution pattern of the latter. Amino acid analyses and UV spectra of the ndividual tryptic peptides indicated that the smaller protein lacked residues 06-116 (Gly-Arg-Gly-Leu-Ser-Leu-Ser-Arg-Phe-Ser-Trp). The deleted portion corres-onds exactly to the amino acid sequence encoded by Exon 5 of the mouse basic pro-ein gene. When our study was essentially complete we discussed the data with r. Kamholz (LMG) who had been working on the human myelin basic protein gene. ased on our data, he synthesized a cDNA probe for this new human BP form and solated the corresponding mRNA, thus confirming our discovery.

In collaboration with Dr. Audrey Stone (LCB) we are completing the investiga-ion of the effect of the phosphorylation of residue 98 on the conformation of ovine myelin basic protein (BBP). Preliminary circular dichroic studies on hetero-eneously phosphorylated BBP showed that the per cent of ordered structure (β-turn lus β structure) increased from 20% to 46% with larger amounts of phosphate on the BP molecule.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 00903-09 LCM

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Purification and Identification of Brain Proteinases and their Cleavage Products

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	Gladys E. Deibler	Chemist	LCM, NIMH
Other:	Marian W. Kies	Chemist	LCM, NIMH

COOPERATING UNITS *(if any)*

Lab. Cell Biology, NIMH; Lab. Experimental Carcinogenesis, NCI;
Lab. Molecular Genetics, NINCDS

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Section on Developmental Neurochemistry

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	1.5	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.)*

Our investigation of human myelin basic protein (HBP) extracted from whole brain has led to the isolation and identification of a new form of HBP with a molecular weight of 17.2 kDa. The more common form is an 18.5 kDa protein. The new form of HBP was successfully separated from HBP-component 3 by a newly developed procedure on FPLC (Fast Protein Liquid Chromotography). Based on recoveries from each step of the procedure we estimated that the new form constituted about 13% of the total HBP. In collaboration with Dr. Henry Krutzsch, NCI, we have shown that both the 17.2 and the 18.5 kDa proteins have blocked amino termini and identical carboxyl termini. When the HPLC elution patterns of the two proteins were compared, we found that four peaks in the chromatogram of the larger protein were missing from the chromatogram of the 17.2 kDa protein. In addition an extra peak was found in the elution pattern of the latter. Amino acid analyses and UV spectra of the individual tryptic peptides indicated that the smaller protein lacked residues 106-116 (Gly-Arg-Gly-Leu-Ser-Leu-Ser-Arg-Phe-Ser-Trp). The deleted portion corresponds exactly to the amino acid sequence encoded by Exon 5 of the mouse basic protein gene. When our study was essentially complete we discussed the data with Dr. Kamholz (LMG) who had been working on the human myelin basic protein gene. Based on our data, he synthesized a cDNA probe for this new human BP form and isolated the corresponding mRNA, thus confirming our discovery.

In collaboration with Dr. Audrey Stone (LCB) we are completing the investigation of the effect of the phosphorylation of residue 98 on the conformation of bovine myelin basic protein (BBP). Preliminary circular dichroic studies on heterogeneously phosphorylated BBP showed that the per cent of ordered structure (β-turn plus β structure) increased from 20% to 46% with larger amounts of phosphate on the BBP molecule.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02217-03 LCM

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Plasticity in the Developing Monkey Visual System

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	Carolyn B. Smith	Chemist	LCM, NIMH
Others:	Louis Sokoloff	Chief	LCM, NIHM
	Susan Herdman	Guest Researcher	LCM, NIMH
	Kentaro Mori	Visiting Fellow	LCM, NIMH
	Ron Tusa	Dept. Neurology, Johns Hopkins Medical School, Baltimore, MD	

COOPERATING UNITS *(if any)*

Dept. Neurology, Johns Hopkins Medical School, Baltimore, MD

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Developmental Neurochemistry Section

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.8	0.5	0.3

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

The postnatal development of the central visual pathways depends on the quality of the visual environment. During the critical period in the primate visual system environmental manipulation can modify the physiological properties of visual cortical cells. The purpose of this project is to study the underlying biochemical events that imbue the nervous system with the property of plasticity. Protein synthesis is a biochemical process which is involved in bringing about changes in morphology, adjustments in growth rates, and remodeling and maintenance of structures. We have therefore used the [^{14}C]leucine method to study the relationships between local plastic changes which occur in the developing monkey visual system and local rates of protein synthesis.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02217-03 LCM

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Plasticity in the Developing Monkey Visual System

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	Carolyn B. Smith	Chemist	LCM, NIMH
Others:	Louis Sokoloff	Chief	LCM, NIHM
	Susan Herdman	Guest Researcher	LCM, NIMH
	Kentaro Mori	Visiting Fellow	LCM, NIMH
	Ron Tusa	Dept. Neurology, Johns Hopkins Medical School, Baltimore, MD	

COOPERATING UNITS *(if any)*

Dept. Neurology, Johns Hopkins Medical School, Baltimore, MD

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Developmental Neurochemistry Section

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.8	0.5	0.3

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

The postnatal development of the central visual pathways depends on the quality of the visual environment. During the critical period in the primate visual system environmental manipulation can modify the physiological properties of visual cortical cells. The purpose of this project is to study the underlying bicohemical events that imbue the nervous system with the property of plasticity. Protein synthesis is a biochemical process which is involved in bringing about changes in morphology, adjustments in growth rates, and remodeling and maintenance of structures. We have therefore used the [^{14}C]leucine method to study the relationships between local plastic changes which occur in the developing monkey visual system and local rates of protein synthesis.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02220-03 LCM

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Regional Biochemical Changes in the Normal Aging Brain

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	Carolyn B. Smith	Chemist	LCM, NIMH
Others:	Louis Sokoloff	Chief	LCM, NIMH
	Kentaro Mori	Visiting Fellow	LCM, NIMH
	Ernesta Palombo	Visiting Fellow	LCM, NIMH
	Hajime Nakanishi	Guest Researcher	LCM, NIMH
	Marian C. Diamond	Professor, Dept. of Physiology-Anatomy, Univ. of California	

COOPERATING UNITS *(if any)*

Department of Physiology-Anatomy, University of California, Berkeley, CA

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Developmental Neurochemistry Section

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.9	0.8	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.)*

Studies are being carried out on the effects of aging on cerebral protein synthesis and glucose utilization in rats. With the application of local methods developed in this laboratory discrete regions of the brain can be examined in normal conscious animals. The regional changes in glucose utilization indicate that entire sensory pathways are affected by the aging process. The fact that similar changes are found in the same pathways with respect to protein synthesis suggests that some of these changes reflect an adaptation of the nervous system to a chronic lack of input. The basis of some of the changes which occur with age can be further examined in studies with pharmacological agents as well as in conjunction with behavioral measurements.

Two such studies have been undertaken. One is a study of the effects of aging on the metabolic responsiveness to the dopaminergic agonist, apomorphine. The other is a study of the effects of environmental enrichment in young adult rats on local metabolic rates. In both of these studies the end point is the local rates of cerebral glucose utilization as determined by the deoxyglucose method.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02220-03 LCM

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

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P.I.:	Carolyn B. Smith	Chemist	LCM, NIMH
Others:	Louis Sokoloff	Chief	LCM, NIMH
	Kentaro Mori	Visiting Fellow	LCM, NIMH
	Ernesta Palombo	Visiting Fellow	LCM, NIMH
	Hajime Nakanishi	Guest Researcher	LCM, NIMH
	Marian C. Diamond	Professor, Dept. of Physiology-Anatomy, Univ. of California	

COOPERATING UNITS *(if any)*

Department of Physiology-Anatomy, University of California, Berkeley, CA

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Developmental Neurochemistry Section

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.9	0.8	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.)*

Studies are being carried out on the effects of aging on cerebral protein synthesis and glucose utilization in rats. With the application of local methods developed in this laboratory discrete regions of the brain can be examined in normal conscious animals. The regional changes in glucose utilization indicate that entire sensory pathways are affected by the aging process. The fact that similar changes are found in the same pathways with respect to protein synthesis suggests that some of these changes reflect an adaptation of the nervous system to a chronic lack of input. The basis of some of the changes which occur with age can be further examined in studies with pharmacological agents as well as in conjunction with behavioral measurements.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02307-01 LCM

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Role of Proteinases in Production and Control of Neuropeptides

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	Marian W. Kies	Chemist	LCM, NIMH
Other:	Gladys E. Deibler	Chemist	LCM, NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Section on Developmental Neurochemistry

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

Early research on CNS proteinases was directed primarily toward their purification and characterization as proteins without much concern for their role in vivo and the identity of their natural substrates. The wide-spread interest in neuropeptides as neuromodulators has shifted the emphasis in CNS proteinase research from enzyme to substrate. It has been postulated that a specific proteinase is responsible for the conversion of inactive precursor to each active peptide as well as a specific peptidase to limit its neuromodulator activity by degradation at the point of peptide release. Whether or not the proteinases/neuropeptides exist in the cell in a one to one relationship (a different proteinase for each neuropeptide), the question of how proteolytic activity is involved in the regulation of neuropeptide activity is an important one.

Several CNS proteinases have been isolated and some have been extensively characterized with respect to their hydrolytic capabilities. There is need for a systematic examination of these purified proteinases and their ability to participate in the post-translational processing of neuropeptide precursor proteins, as well as their ability to terminate neuropeptide activity. Conversely, crude preparations with known ability to degrade a given neuropeptide need to be purified to establish their specificity with regard to that neuropeptide or to identify them with other peptidases which have already been purified or characterized.

What we propose to do, initially, is to isolate some brain proteinases which have been described on the basis of molecular weights, pH optima, activators, inhibitors and specific ion requirements but not associated with any of the known neuropeptide/precursor systems and examine their peptide bond specificity with one or more purified CNS proteins or peptides of known sequence.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02307-01 LCM

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

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PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.:	Marian W. Kies	Chemist	LCM, NIMH
Other:	Gladys E. Deibler	Chemist	LCM, NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Section on Developmental Neurochemistry

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

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What we propose to do, initially, is to isolate some brain proteinases which have been described on the basis of molecular weights, pH optima, activators, inhibitors and specific ion requirements but not associated with any of the known neuropeptide/precursor systems and examine their peptide bond specificity with one or more purified CNS proteins or peptides of known sequence.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 02308-01 LCM

PERIOD COVERED
October 1, 1985 to September 30, 1986

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Growth and Development of Dopaminergic Neurons

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.: Bernard F. Driscoll Research Biologist LCM, NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH
Laboratory of Cerebral Metabolism

SECTION
Developmental Neurochemistry Section

INSTITUTE AND LOCATION
NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

Development of central nervous system pathways involves the action of soluble factors on target cells and interactions between various cell types. One of the best defined CNS pathways is the nigrostriatal pathway. To examine events involved in the formation of this pathway, development of dopaminergic neurons from the embryonic rat mesencephalon was examined in dissociated cell cultures.

To maintain maximum control over the cell environment, cultures were grown in chemically defined medium containing the minimum constituents needed for cell survival and development. When grown under these conditions, neurons exhibit neurite extension after several hours and eventually display extensive neuritic outgrowth. In contrast to cells grown in serum, the cell bodies of these neurons remain dispersed on the culture dish and neurites grow separately forming a fine mesh. Due to these growth characteristics, individual cell bodies and neurites can be identified in developed cultures. Development of the dopaminergic neurons was determined by uptake of exogenous, labelled dopamine.

When mesencephalic neurons were grown in the presence of neurons from specific regions of the brain, development of the dopaminergic neurons was greatest when they were co-cultured with neurons from the striatum. These neurons are the normal in vivo target cells of the mesencephalic dopaminergic neurons. Under specifically defined culture conditions, it appears that the enhanced development of the dopaminergic neurons is due to the presence of striatal neurons and is not dependent on the presence of other striatal cell types. However, enhanced development of the dopaminergic neurons can be induced under other culture conditions and this development is unrelated to the presence of target (striatal) neurons. This latter development is probably be due to the presence of a critical number or particular type of glial cells in the culture.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02308-01 LCM

PERIOD COVERED

October 1, 1985 to September 30, 1986

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

Growth and Development of Dopaminergic Neurons

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

P.I.: Bernard F. Driscoll Research Biologist LCM, NIMH

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Developmental Neurochemistry Section

INSTITUTE AND LOCATION

NIMH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	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.)*

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 00507-04 LCM

PERIOD COVERED: October 1, 1985 to September 30, 1986

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

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Robert M. Cohen, M.D., Ph.D., Chief, CBI, LCM, NIMH

COOPERATING UNITS *(if any)* Clinical Neuroscience Branch, NIMH; Biological Psychiatry Branch, NIMH; Neuropsychiatry Branch, NIMH; Experimental Therapeutics Branch, NINCDS; St. Elizabeths Hosp., NIMH; Nuclear Medicine, CC, NIH; Child Psychiatry Branch, NIMH

LAB/BRANCH: Laboratory of Cerebral Metabolism

SECTION: Section on Clinical Brain Imaging

INSTITUTE AND LOCATION: The National Institute of Mental Health
9000 Rockville Pike, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
7.8	4.9	2.9

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 major areas of effort in this project have been (1) To refine existing methodologies for the study of cortical functioning based on positron emission tomography (PET); (2) To develop new tracers or other approaches for the study of neurotransmitter function in normal and abnormal physiology; (3) To apply what tracer methodologies we have available to the study of neuropsychiatric disorders. To these ends the following achievements are notable. Our study of schizophrenic patients, on and off neuroleptics, receiving repeated somatosensory stimulation (SS) during metabolic measurement in comparison to normals by FDG-PET i.e., the study of regional brain activities through observations of regional glucose metabolic rates (lCMRglu's) as calculated from PET scan measurements of ^{18}F-deoxyglucose accumulation has been completed and differences reported. This work provided weak support for the existence of "hypofrontality" in schizophrenia, and did not find any improvement in hypofrontality when patients were treated. We have completed the collection of data on the study of two additional behavioral paradigms with FDG-PET. These studies were of auditory continuous performance (CPT), and rest (REST) and totaled 43 normals. Altogether the data allowed us to develop a statistical approach to the handling of PET data that is both sensitive to the small changes observed upon behavioral changes while maintaining reliability. It provides evidence that SS may not be a good condition for observing hypofrontality except perhaps within one particular area of the frontal cortex. Most importantly, the data from this comparison strongly supports the heterogenity of the frontal cortex and the need to examine very carefully the detailed pattern of metabolism in the frontal cortex if we are to understand the physiology and pathophysiology of behavior.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 MH 00507-04 LCM

PERIOD COVERED: October 1, 1985 to September 30, 1986

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

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

Robert M. Cohen, M.D., Ph.D., Chief, CBI, LCM, NIMH

COOPERATING UNITS *(if any)*: Clinical Neuroscience Branch, NIMH; Biological Psychiatry Branch, NIMH; Neuropsychiatry Branch, NIMH; Experimental Therapeutics Branch, NINCDS; St. Elizabeths Hosp., NIMH; Nuclear Medicine, CC, NIH; Child Psychiatry Branch, NIMH

LAB/BRANCH: Laboratory of Cerebral Metabolism

SECTION: Section on Clinical Brain Imaging

INSTITUTE AND LOCATION: The National Institute of Mental Health
9000 Rockville Pike, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
7.8	4.9	2.9

CHECK APPROPRIATE BOX(ES)

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

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DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02296-01 LCM

PERIOD COVERED

October 1, 1985 through September 30, 1986

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

Positron Tomographic Imaging of Dopaminergic Systems and their Turnover

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

C. C. Chiueh Special Expert LCM NIMH

COOPERATING UNITS *(if any)*

Nuclear Medicine Dept., CC, NIH; Office of the Director, IRP, NINCDS; and McMaster University Medical Centre, Hamilton, Ontario, Canada.

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Section on Clinical Brain Imaging

INSTITUTE AND LOCATION

The National Institute of Mental Health, Bethesda, Maryland

TOTAL MAN-YEARS:	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.)*

We have previously established a neurochemical basis for the use of **L-6-^{18}F-dopa** as a presynaptic imaging ligand for **brain dopaminergic systems.** A potential clinical use of this **positron emission tomographic ligand** in visualizing and determining degrees of brain damage in **Parkinson's disease** was demonstrated in the present preclinical study by using the MPTP-induced **primate model of parkinsonism.** Despite a high background activity due to an accumulation of a methoxylated metabolite of L-dopa, both in vivo positron emission tomographic and ex vivo autoradiographic imaging procedures showed that the depletion of striatal dopamine and/or the decrease in decarboxylase activity can be assessed quantitatively by using this presynaptic imaging ligand. The present results indicated that both striatal dopamine and its synthetic enzymes were absent in the severely lesioned parkinsonian animals. The striatal ^{18}F-dopaminergic activity calculated by the positron emission tomographic **brain imaging procedure** in vivo correlated with the content of endogenous dopamine measured postmortem in each subject. The ex vivo ^{14}C-L-dopa autoradiographic imaging revealed dopaminergic systems not only in the caudate nucleus, but also in the nucleus accumbens, the paraventricular nucleus and the median eminence. Thus, the positron emission tomographic imaging procedure for brain dopamine could be simulated in small experimental animals in order to improve and standardize this procedure for future clinical studies in **diagnosing subclinical cases of Parkinson's disease.** It is proposed to investigate the **safety margin** of this positron emitting presynaptic ligand in order to establish this brain dopamine imaging procedure in the NIH clinical center for investigating dopaminergic mechanisms in **neuropsychiatric disorders** and understanding the mental and/or motor functions of dopamine.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 MH 02296-01 LCM

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October 1, 1985 through September 30, 1986

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C. C. Chiueh Special Expert LCM NIMH

COOPERATING UNITS *(if any)*

Nuclear Medicine Dept., CC, NIH; Office of the Director, IRP, NINCDS; and McMaster University Medical Centre, Hamilton, Ontario, Canada.

LAB/BRANCH

Laboratory of Cerebral Metabolism

SECTION

Section on Clinical Brain Imaging

INSTITUTE AND LOCATION

The National Institute of Mental Health, Bethesda, Maryland

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.0	2.5	0.5

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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