National Eye Institute.
Report.

ANNUAL REPORT
National Eye Institute
October 1, 1984 - September 30, 1985

REPORT OF THE SCIENTIFIC DIRECTOR
Jin H. Kinoshita, Ph.D.

During this past year, the problems associated with the reduction in the personnel staff have forced the curtailment of some intramural research projects and seriously affected others. Nevertheless, it is impressive that significant progress has been achieved in many research areas. To illustrate this point four studies will be cited in this report even though there are several other intramural studies which are equally impressive.

For a number of years Dr. Robert Nussenblatt, Dr. Igal Gery and their associates have been developing experimental animals models which simulate the inflammatory eye diseases known as uveitis. The most promising approach was found to be the injection of a purified retinal protein, identified as S antigen, into Lewis rats, guinea pigs and monkeys. Animals immunized with S antigen developed clinical anterior and posterior uveitis which was confirmed by histology. The monkey model closely resembled the disease found in posterior uveitis patients. Additional experimental study suggested to the group that T-cells were involved in this ocular inflammatory process. Since cyclosporine, a complex peptide isolated from a certain fungus, was known to suppress T-cell activity, the NEI scientists thought of the possibility that cyclosporine may alleviate this inflammatory eye process. Remarkably the cyclosporine treatment completely prevented the S-antigen induced uveitis in animals.

The laboratory studies encouraged Dr. Nussenblatt to test the effectiveness of cyclosporine in patients with various types of uveitis. Preliminary studies suggested that patients with the inflammatory disorder known as Behcet's disease were particularly responsive to cyclosporine treatment in that the inflammatory process was dramatically alleviated. These findings served as the basis for a full-scale randomized clinical trial of cyclosporine as a method of treatment of Behcet's patients. Dr. Nussenblatt arranged to have this trial conducted as a multi-center study in Japan where there is greater prevalence of these Behcet's cases than in this country. This study was concluded recently and positive results were obtained indicating that cyclosporine is indeed effective against this form of uveitis. Thus, the series of studies which began in the laboratory has led to the development of a treatment of an inflammatory eye disease where no specific treatment was known before.

For his contributions for the development of cyclosporine as a therapeutic agent of uveitis Dr. Robert Nussenblatt will be honored by the Japanese Ophthalmological Society in 1986.

Dr. Piatigorsky and associates of the LMDB have been developing transgenic mice which have been used in an exciting study that potentially has clinical relevance. These mice permit the analysis of DNA sequences which are responsible for the expression, tissue-specificity and developmental program of gene expression. In their investigations they identified numerous putative regulatory regions of the genes for a specific lens protein, the αA-crystallin. Furthermore, transient expression experiments using explanted lens epithelia have provided evidence that these DNA sequences are indeed responsible for the tissue-specific expression of the crystallin genes. Recently, they created a DNA containing the αA-crystallin gene promoter (only 364 nucleotides) fused with the bacterial chloramphenicol acetyltransferase gene (CAT). They injected this recombinant DNA into the nucleus of a fertilized mouse egg and produced a male transgenic mouse which had CAT activity in its ocular lens and only in the lens. None of the 9 other tissues examined contained CAT activity. This clearly permits further analysis of the molecular nature of tissue-specific crystallin gene expression at the level of the whole organism. Moreover, it kindles hope for eventual gene therapy of ocular diseases.

For his many important contributions of the application of molecular biology to the eye, Dr. Piatigorsky has been designated as the recipient of the 1986 Friedenwald Award, one of the prestigious awards presented by the Association for Research in Vision and Ophthalmology.

Major advances in the study of gyrate atrophy have been made by a team of scientists led by Dr. Muriel Kaiser-Kupfer. Gyrate atrophy is a rare hereditary disease which leads to the degeneration of the retina and choroid. This team of scientists has shown that this disorder is caused by a deficiency of the enzyme ornithine aminotransferase (OAT) which results in a hyperornithinia in these patients. Dr. Kaiser-Kupfer has shown that diets which restrict the sources of ornithine seem to protect and even improve visual function.

Stimulated by these clinical studies, Dr. George Inana and his colleagues began examining the gyrate atrophy problem using DNA technology. They have been successful in isolating a cDNA clone for human OAT. With this probe they are studying the nature of the OAT gene defect in gyrate atrophy patients. This study is an example of how rapidly a clinical problem can be attacked with the most modern of research tools because of the unique setting of the intramural program which fosters the interactions of scientists from many disciplines.

For the development of the first cDNA probe to study an ocular disease Dr. George Inana will be honored as the principal guest lecturer at the Proceedings of the Japanese Chapter of the International Society of Eye Research in Sendai, Japan in 1985.

Dr. Wurtz has pioneered studies on the understanding of how the brain uses visual information to produce eye movements. His recent work, using old world monkeys as a model system, has had two facets. First, he has extended his analyses of the brain circuits that produce the rapid or saccadic eye movements that move the eye quickly from one part of the visual field to another. His studies were the first to recognize that the basal ganglia of the brain participated in controlling saccadic eye movements. The basal ganglia produce a tonic inhibition on the saccadic control system of the brainstem, the superior colliculus. In addition his recent findings revealed that the neuronal transmitter is likely to be GABA since he has been able to inhibit or facilitate eye movements by injecting minute quantities of GABA agonists or antagonists into the terminal area of basal ganglia fibers in the superior colliculus. Thus, a major new control system acting on the initiation of saccadic eye movements has been revealed. His second series of experiments has been on a second type of eye movement, the pursuit eye movements that allow the eye to track moving targets. Dr. Wurtz's group has shown that these movements are normally dependent for their visual input on a tiny area of cerebral cortex that is devoted to processing of visual motion information. Furthermore, minute damage produced by microliter injections of a neurotoxic chemical into adjacent regions produces the directional deficit in pursuit eye movements seen in human patients with cerebral damage. These experiments show for the first time the precise localization and function of the cerebral cortical areas upon which pursuit eye movements are dependent.

For these accomplishments Dr. Wurtz is being honored by the European Neuroscience Association which has designated him to present the Gordon Holmes Lecture at the meeting of the Association in September, 1985.

Although the intramural program faces difficult times ahead because of restrictions in budget, personnel and space it is encouraging that accomplishments like those cited here can be achieved. This is a tribute to the intramural scientists with their talents and enthusiasm who devote their lives to dispel our ignorance in many problems related to the eye.

ANNUAL REPORT
NATIONAL EYE INSTITUTE
October 1, 1984 - September 30, 1985

REPORT OF THE DEPUTY CLINICAL DIRECTOR

Robert B. Nussenblatt, M.D.

The Clinical Branch of the NEI has seen a continuous evolution of its clinical and research programs. The year saw a maturing of various projects. The clinical studies of the Eye Institute made it one of the busiest outpatient services at the Clinical Center. The Branch is composed of five Sections; each with its own Section head: Section on Clinical Ophthalmic Immunology, Robert B. Nussenblatt, M.D., Section on Neuro-ophthalmology, Jon Currie, M.D. (Acting), Section on Ophthalmic Genetics and Pediatric Ophthalmology, Muriel I. Kaiser-Kupfer, M.D., Section on Visual Processing, Francisco deMonasterio, M.D., D.Sc., and Retinal and Vitreal Disease Section, Robert B. Nussenblatt, M.D. (Acting).

The Section on Clinical Ophthalmic Immunology investigated questions concerning ocular inflammatory disease utilizing both clinical and laboratory approaches. A significant effort has been devoted to the ocular manifestations of the acquired immunodeficiency syndrome (AIDS). HTLV-3, the putative viral cause of AIDS, was isolated from the tears of AIDS patients. Further, the virus has been localized to the conjunctival epithelium, suggesting that this may be the ocular repository of the virus. Therapy with a new drug DHPG, for the cytomegalovirus infection of the retina, so often seen in immunocompromised hosts as AIDS patients, has begun as a collaborative effort with researchers in the Allergy and Infectious Diseases Institute. The understanding of basic mechanisms in ocular inflammatory disease has been furthered by the demonstration of Ia antigen expression on the vascular endothelium in the eye, and as well on other ocular cells such as Muller cells, RPE, and stromacytes cells not usually part of the immune system. This antigen expression may suggest a role for these cells in the localization of the immune response to the eye. Further work on immunomodulation has centered about the Cyclosporines, from better characterizing the potential adverse effects of CsA and how to reverse them to the use of the newer cyclosporines, such as CsG, thought not to be nephrotoxic. The first masked randomized corneal transplant study in the U.S. using Cyclosporine has just begun.

The Neuro-ophthalmology Section has had a long-standing interest in oculo-motor disorders, with detailed evaluation centering around such entities as congenital nystagumes, Parinaud's syndrome, and ocular motor palsies. It has recently been found that a single dose of clonazepam can be used to reduce or eliminate for a short time the intensity of congenital nystagmus, thus allowing for an assessment of underlying visual acuity. Newer methodology has been used to better correlate clinical observations with central nervous system lesions. The use of positron emission scanning (PET) and magnetic resonance scanning have helped to correlate anatomic alterations to the clinical observation. The Section continues to build one of the most valuable videotape and oculographic libraries in the field of neuro-ophthalmology.

Scientists in the Section on Ophthalmic Genetics and Pediatric Ophthalmology are continuing to recruit and evaluate patients with a variety of inherited ocular conditions. Of particular note are those patients with gyrate atrophy. Skin fibroblasts of these patients are assayed in vitro for the presence of ornithine aminotransferase activity, while these patients are given a trial of pyridoxine to evaluate its effect on serum ornithine, the lowering of which is thought to arrest or possibly improve the condition. The monitoring and documentation of lens opacities has been advanced with the introduction of the Scheimpflug camera. Researchers in this Section actively participate in the NIH Interinstitute Medical Genetics Program. Because of the high frequency of ocular involvement in many of the cases, almost all patients were evaluated by the Clinical Branch staff or were discussed in consultation.

The Section on Retinal and Vitreal Disease has been participating in a multicenter double masked randomized study evaluating the effects of the aldose reductase inhibitor, sorbinol on diabetic retinopathy. Additionally, a randomized trial is underway to evaluate the effectiveness of vitamin therapy and protection of the retina from exposure to right below 500 nanometers in preventing senile macular degeneration.

The Section on Visual Processing provides the supportive electrophysiologic and psychophysical testing for both inpatients and outpatients, as well as those patients seen in consultation. In addition, the Section has maintained active research activities. This includes the use of spatial contrast sensitivity in retinal and neuro-ophthalmic disease, as well as studying the neuro-ophthalmology of the human electroretinogram. As well, the mapping of retinal ganglion cell types in the retina and the study of the central nervous system's component to the visual system are being examined.

The Clinical Branch continues to be at the cutting edge of many areas of ophthalmic research. The union of basic and clinical research continues to yield important observations.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 EY 00001-03 CB

PERIOD COVERED
October 1, 1984 to September 30, 1985

TITLE OF PROJECT (Do not exceed the space provided. Do not use abbreviations unless they are well known.)
Activity labeling with 2-deoxyglucose of the visual system of primates

PRINCIPAL INVESTIGATOR (List other professional personnel below the Principal Investigator that are participating in the project.)

PI:	Francisco M. de Monasterio	M.D., D.Sc.	Chief, SVP	CB, NEI
Others:	Stanley J. Schein	M.D., Ph.D.	Guest Worker	Mass Eye and Ear
	Edna P. McCrane	B.S.	Biologist	CB, NEI

COOPERATING UNITS (If any)
Howe Laboratory of Neuro-ophthalmology, Massachusettes Eye and Ear Infirmary, Harvard Medical School

LAB/BRANCH
Clinical Branch

SECTION
Section on Visual Processing

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.70	0.20	0.50

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

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

Sequential double-labeling with 14C-2DG for one stimulational condition and 3H-2DG for a second allows direct comparison of patterns of activity within the same brain sections. We developed methods for separation of the 3H and 14C images directly on film.

We hypothesized the existence of a lag between change in stimulus and corresponding change in 2DG uptake. At the termination of exercise, the increased metabolic activity in muscle does not cease instantly. Increased metabolic activitiy continues for some time, a period of "cool-down". Conversely, when we begin to exercise, there is a "warm-up" period before glucose utilization reaches its (high) steady-state level. To demonstrate this phenomena in brain, we took advantage of the ocular-dominance system in macaque striate cortex. One eye was occluded for 30 minutes; then an occluder was placed in the other eye as well, and an injection of 2DG was given at the same time. Thus, during the period of exposure to 2DG, the animal received no visual stimulation. Nonetheless, the autoradiograms of striate cortex show striking ocular dominance patterns, including stripes in layer IV and activation of half of the stripes of "puff" in layers II and III. Thus, the lag was confirmed, at least for cool-down.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00006-14 CB

October 1, 1984 to September 30, 1985

Measurement of Color Vision

PI:	Ralph D. Gunkel	O.D.	Ophthalmic Physicist	CB, NEI
Others:	Monique Roy	M.D.	Visiting Scientist	CB, NEI
	Marvin J. Podgor	M.D.	Biometrist	CB, NEI

None

Clinical Branch

Section on Visual Processing

NEI, NIH, Bethesda, Maryland 20892

0.70 0.70 0.0

One or more kinds of color vision tests were given to patients and subjects registered in this and related projects.

In addition to the color tests, dark adaptation studies with measurements of rod and cone thresholds were made on many patients, particularly those who were beginning or maintaining medications thought to affect visual function.

Tests were conducted on 319 patients during the year, including some normal controls. It was found that the Hardy-Rand-Rittler Pseudoisochromatic Plates and the Farnsworth Panel D-15 are not sufficiently sensitive to reveal subtle defects in color vision, so most of the color tests were done with the Lanthony Desaturated Panel D-15, the Farnsworth-Munsell 100-Hue tst, and the Gunkel Chromagraph. Three kinds of tests were used in an effort to determine their relative consistency, suitability, sensitivity, and validity for use with patients having different types and degrees of illness.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00011-11 CB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Pigment Dispersion With and Without Glaucoma

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

PI:	Muriel I. Kaiser-Kupfer	M.D.	Head, Section on Ophthalmic Genetics and Pediatric Ophthalmology	CB, NEI
Others:	Carl Kupfer	M.D.	Director	NEI
	Lessie McCain	R.N.	Clinical Technician	CB, NEI
	Manuel Datiles	M.D.	Visiting Scientist	CB, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Branch

SECTION

Section on Ophthalmic Genetics and Pediatric Ophthalmology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
.5	.2	.3

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 purpose of this project is to compare patients with and without glaucoma having pigment dispersion syndrome. The data acquired may enable a determination of the risk of patients with pigment dispersion syndrome to developing glaucoma as well as add to understanding of the pathology of the disease.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 EY 00059-07 CB

PERIOD COVERED

October 1, 1984 to September 30, 1985

Electrophysiological and Psychophysical Evaluation of Retinal Disorders

PI:	Francisco M. de Monasterio	M.D., D.Sc.	Chief, SVP	CB, NEI
Others:	Rafael C. Caruso	M.D.	Expert	CB, NEI
	Kent E. Higgins	Ph.D.	Expert	CB, NEI
	Ralph D. Gunkel	O.D.	Ophthalmic Physicist	CB, NEI
	Myles J. Jaffe	O.D.	Staff Fellow	CB, NEI

Other sections of the Clinical Branch, NEI

Clinical Branch

Section on Visual Processing

NEI, NIH, Bethesda, Maryland 20892

2.20 1.05 1.15

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

(a1) Minors

(a2) Interviews

This is a general support, service-providing project covering two major activities. One activity includes service-providing studies of visual function for the supportive or collaborative diagnosis, evaluation, and follow-up of patients with inflammatory, degenerative, toxic, or congenital disorders. These activities include all of the routine electrophysiological and psychophysical testing of inpatients, outpatients, and referred consult cases seen in the NEI's Eye Clinic. In this fiscal year about 2300 tests will be performed with a total of ca. 14,000 tests performed over the last six years. In addition, these activities also provide most of the current "specialized" testing on visual sensory neural function of patients, often under collaborative arrangements with other sections of the Clinical Branch.

The other activity involves the development of new tests for clinical studies using non-invasive electrophysiological and psychophysical measurements. Such tests, developed under this project, are, upon successful completion, assigned to separate projects for normative and clinically applied studies. Efforts continue toward the development of tests centered around a system of retinal-image stabilization which is currently being used for studies of selected cases.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00060-09 CB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Visual Function and Ocular Pigmentation in Albinism

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

PI:	Muriel I. Kaiser-Kupfer	M.D.	Head, Section on Ophthalmic Genetics and Pediatric Ophthalmology	CB, NEI
Others:	Lessie McCain	R.N.	Clinical Technician	CB, NEI
	Rafael Caruso	M.D.	Expert	CB, NEI
	Linda Wang	B.S.	Health Technician	CB, NEI
	Patricia Mercer	B.S.	Clinical Technician	CB, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Branch

SECTION

Section on Ophthalmic Genetics and Pediatric Ophthalmology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20205

TOTAL MAN YEARS	PROFESSIONAL	OTHER
.65	.35	.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.)*

Patients with hypomelanotic disorders such as ocular albinism, oculocutaneous albinism, Chediak-Higashi disease, Hermansky-Pudlak syndrome, and iris transillumination defects are being recruited to determine visual function in these conditions and to evaluate its course over time. Family members are evaluated to attempt to determine factors which may identify the heterozygous state.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00062-09 CB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Irido-Corneal-Endothelial (ICE) Syndrome

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

PI:	Muriel I. Kaiser-Kupfer	M.D.	Head, Section on Ophthalmic Genetics and Pediatric Ophthalmology	CB, NEI
Others:	Carl Kupfer	M.D.	Director	NEI
	Lessie McCain	R.N.	Clinical Technician	CB, NEI
	Manuel Datiles	M.D.	Visiting Scientist	CB, NEI

COOPERATING UNITS *(if any)*

LAB BRANCH

Clinical Branch

SECTION

Section on Ophthalmic Genetics and Pediatric Ophthalmology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
.25	.25	0.5

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

Patients are being recruited with The Irido-Corneal Endothelial (ICE Syndrome) with or without associated corneal disease. Information is being gathered to evaluate the clinical features and course of the disease process and to investigate aqueous humor dynamics in both affected and unaffected eyes.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 EY 00063-07 CB

October 1, 1984 to September 30, 1985

Acquired and Congenital Color Vision Deficiencies: Mechanisms and Diagnosis

PI:	Kenneth B. Knoblauch	Ph.D.	Staff Fellow	CB, NEI
Others:	Francisco M. de Monasterio	M.D., D.Sc.	Chief, SVP	CB, NEI
	Kent E. Higgins	Ph.D.	Expert	CB, NEI

Clinical Branch

Section on Visual Processing

NEI, NIH, Bethesda, Maryland 20892

1.10 1.10 0.0

x

This project involves the use of psychophysical tests to study cone function in individuals with color vision defects, with special emphasis on acquired deficiencies. First, a saturation discrimination task is used to determine the hue sensitivity of normal volunteers and patients with abnormal color vision. Second, we are examining whether we can specify a set of illumination conditions that would optimize the ability to distinguish individuals with normal color vision and those with acquired defects resulting from early stages of retinal disease. For this purpose, we have documented the interaction of age and illumination level on the performance of the FM 100-hue test on a normal population. Third, we have collected normative data on the effect of aging on the TNO-tritan test, a quich test for tritan type defects.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 EY 00065-08 CB

October 1, 1984 to September 30, 1985

Electrophysiological Studies of the Visual System of Primates

PI:	Francisco M. de Monasterio	M.D., D.Sc.	Chief, SVP	CB, NEI
Others:	Stanley J. Schein	M.D., Ph.D.	Guest Worker	Mass Eye and Ear
	Edna P. McCrane	B.S.	Biologist	CB, NEI

Howe Laboratory of Neuro-ophthalmology, Massachusettes Eye and Ear Infirmary, Harvard Medical School

Clinical Branch

Section on Visual Processing

NEI, NIH, Bethesda, Maryland 20892

0.30 0.25 0.05

We have investigated the mapping of the two major classes of retinal ganglion cells, color-opponent and broad-band, onto striate cortex (VI) of macaque. There is a one to one relationship between color-opponent retinal ganglion cells and parvocellular cells of the Lateral Geniculate Nucleus (LGN), which we call the P-cell system. A similar relationship holds for broad-band ganglion cells and magnocellular cells of the LGN, which we call the M-cell system. There is a nearly constant number of P-cells projecting to each mm^2 of VI, whereas that for M-cells increases with eccentricity. In VI the cytochrome-oxidase puffs have been thought to define a module of function. Our results indicate that these units are better described as a P-cell module. The VI-point-image referes to the maximal area activated by a point in visual space. A constant number of M-cells project to the point-image area, independent of eccentricity.

In single-cell recordings from ganglion cells of macaque retina we have examined the effects of the onset and offset of moderately intense, large field backgrounds. Broad-band (color non-opponent) cells show strong transient desensitizations to both onset and offset of the background lights. In contrast, the behavior of color-opponent ganglion cells varied with the cell subtype. Blue-center cells showed large desensitizations at the onset and offset (transient tritanopia) of the background, while green-center cells showed very weak desensitization. Red-center and yellow-center cells showed an intermediate behavior.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00075-07 CB

PERIOD COVERED: October 1, 1984 to September 30, 1985

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*: Immune Functions in Ocular Diseases of Obscure Etiology

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

PI:	Robert B. Nussenblatt	M.D.	Head, Section on Clinical Ophthalmic Immunology	CB, NEI
Others:	Alan G. Palestine	M.D.	Staff Ophthalmologist	CB, NEI
	Chi-Chao Chan	M.D.	Staff Ophthalmologist	CB, NEI
	William Leake	M.S.	Biologist	CB, NEI
	John J. Hooks	Ph.D.	Microbiologist	CB, NEI

COOPERATING UNITS *(if any)*:

LAB/BRANCH: Clinical Branch

SECTION: Section on Ophthalmic Immunology

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

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.6	0.5	0.1

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.)*

In vitro cellular immune functions and lymphocyte subsets are being studied in a masked method in patients with ocular toxoplasmosis, pars planitis, Behcet's disease, geographic choroiditis, and chorioretinitis of unknown origin. Crude ocular antigens, as well as the purified uveitogenic soluble antigen (S-antigen) of the retina, are being used in a lymphocyte microculture technique to evaluate the presence of cellular immune memory to ocular tissues. A subgroup of patients with posterior uveitis has been identified as having this immunologic memory. Lymphocyte subsets in the blood and in the eye are being defined in these patients by monoclonal antibodies. These results shed light on the basic mechanisms of uveitis and may be used as a guide for specific immunologic therapy. In a small group of selected patients, chorioretinal biopsies are performed to evaluate the on-going ocular immune response.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00083-08 CB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Gyrate Atrophy of the Choroid and Retina

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

PI:	Muriel I. Kaiser-Kupfer	M.D.	Head, Section on Ophthalmic Genetics and Pediatric Ophthalmology	CB, NEI
Others:	Lessie McCain	R.N.	Clinical Technician	CB, NEI
	Francisco de Monasterio	M.D.	Head, Section on Visual Processing	CB, NEI
	Linda Wang	B.S.	Health Technician	CB, NEI

COOPERATING UNITS *(if any)*

Department of Pediatrics and Medicine, The Johns Hopkins University School of Medicine, Baltimore, Maryland (David Valle)

LAB/BRANCH

Clinical Branch

SECTION

Section on Ophthalmic Genetics and Pediatric Ophthalmology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
.9	.4	.5

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.)*

Patients with gyrate atrophy of the choroid and retina are examined systematically to confirm the diagnosis. Skin fibroblasts of affected patients and family members are grown in tissue culture and assayed for ornithine aminotransferase activity. The results will be evaluated for correlation with the presence of homo- or heterozygosity for the disease trait. Patients will be given a trial of pyridoxine to see if serum concentration of ornithine can be reduced, and, if so, the patient will be classified as a "responder," and treatment with pyridoxine will be continued. Nonresponder and responder patients will be placed on a low arginine, low protein diet with supplemental amino acids and observed for an arrest or improvement of their disease. If patients are not considered eligible for the diet or if they appear unable to comply with the dietary regimen they will be followed to record the natural progress of the condition. Patients with other forms of retinal degeneration, such as retinitis pigmentosa, fundus flavimaculatus, juvenile retinoschisis, are also examined and their courses are compared with gyrate atrophy patients.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00084-07 CB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Anterior Chamber Anomalies Associated with Glaucoma or Ocular Hypertension

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

PI:	Carl Kupfer	M.D.	Director	NEI
Others:	Muriel I. Kaiser-Kupfer	M.D.	Head, Section on Ophthalmic Genetics and Pediatric Ophthalmology	CB, NEI
	Lessie McCain	R.N.	Clinical Technician	CB, NEI
	Manuel B. Datiles	M.D.	Visiting Scientist	CB, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Branch

SECTION

Section on Ophthalmic Genetics and Pediatric Ophthalmology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.70	0.40	0.30

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.)*

With recent embryological research indicating the role of the neural crest in contributing to all connective tissues anterior to the lens epithelium, the group of developmental anomalies of the anterior chamber with glaucoma or ocular hypertension is being reviewed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00086-07 CB

PERIOD COVERED
October 1, 1984 to September 30, 1985

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Contributions to Ophthalmic Pathology and Systemic Disease

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

PI: David G. Cogan M.D. Head, Section on Neuro-ophthalmology CB, NEI

Others: Toichiro Kuwabara M.D. Chief, Laboratory of Ophthalmic Pathology LOP, NEI

COOPERATING UNITS *(if any)*
Clinical Neuro-psychology Branch, NINCDS (E. D. Witt); Section on Neuro-Anatomy, Yale University School of Medicine, New Haven, CT (P. S. Goldman-Rakic)

LAB BRANCH
Clinical Branch

SECTION
Section on Neuro-ophthalmology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.5	0.3	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 pathologic effects of thiamine deficiency were studied in the monkey brain and correlated with ocular motor function, as a model for Wernicke's encephalopathy in the human.

A study was made of the development of blood vessels in the fetal and neonatal human retina, with particular reference to changes in angioblasts and accessory cells.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00089-07 CB

PERIOD COVERED
October 1, 1984 to September 30, 1985

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

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

PI:	David G. Cogan,	M.D.	Head, Section on Neuro-ophthalmology	CB, NEI
Others:	Jon N. Currie,	M.D.	Acting Head, Section on Neuro-ophthalmology	CB, NEI
	Linda R. Dagi	M.D.	Staff Fellow	CB, NEI
	Georgia A. Chrousos	M.D.	Guest Worker	CB, NEI
	Toichiro Kuwabara	M.D.	Chief, Laboratory of Experimental Pathology	LOP, NEI

COOPERATING UNITS *(if any)*
Section on Clinical Neurosurgery, National Institute of Neurological and Communicative Disorders and Stroke (E. Oldfield)

LAB/BRANCH
Clinical Branch

SECTION
Section on Neuro-ophthalmology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.5	0.4	.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 continued into the ocular motor abnormalities in Gaucher's disease, abetalipoproteinemia and Nieman Pick variant (DAF syndrome) in an attempt to more clearly delineate subgroups of each syndrome and to determine underlying deficits in neural control.

Marked tortuosity of blood vessels and deposition of ceramide in the vessel wall pericytes was demonstrated in orbital vessels of all sizes in a patient with Fabry disease. Embolic branch retinal artery oclusion without vasculitis was described in a patient with Churg-Strauss vasculitis.

Retinal toxicity was described as a complication of intracarotid infusion of BCNU (carmustine) and cis-platinum for treatment of primary brain gliomas. This toxicity was markedly reduced by careful positioning of the infusion catheter beyond the ophthalmic artery.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: ZO1 EY 00092-07 CB

PERIOD COVERED
October 1, 1984 to September 30, 1985

TITLE OF PROJECT *(80 characters or less Title must fit on one line between the borders)*
HLA, ABO, and B-cell Alloantigens and Ocular Inflammatory Disease

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator) (Name, title, laboratory and institute affiliation)*
PI: Robert B. Nussenblatt, M.D. Head, Section on Clinical Ophthalmic Immunology CB, NEI

COOPERATING UNITS *(if any)*
Bureau of Biologics, FDA (Kamal Mittal, Ph.D.)

LAB/BRANCH
Clinical Branch

SECTION
Section on Ophthalmic Immunology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.03	0.03	0.0

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)*

Patients with ocular toxoplasmosis, pars planitis, Behcet's disease, chorioretinitis of unknown origin, are being studied to determine the phenotype frequency of the HLA, ABO, and B-cell alloantigens. Because the B-cell alloantigens or DR antigens are thought to play a role in the immunologic response to antigens, these findings will complement other immune uveitis studies being simultaneously carried out.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00094-07 CB

PERIOD COVERED
October 1, 1984 to September 30, 1985

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Immune Mechanisms in Experimental Autoimmune Uveitis

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

PI:	Robert B. Nussenblatt	M.D.	Head, Section on Clinical Ophthalmic Immunology	CB, NEI
Others:	Igal Gery	Ph.D.	Visiting Scientist	LVR, NEI
	William Leake	M.S.	Biologist	CB, NEI
	Chi-Chao Chan	M.D.	Staff Ophthalmologist	CB, NEI
	Alan G. Palestine	M.D.	Staff Ophthalmologist	CB, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Branch

SECTION
Section on Ophthalmic Immunology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
2.15	2.06	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.)*

Lewis rats and non-human primates, immunized at a site distant to the eye with the retinal soluble antigen (S-antigen) in complete Freund's adjuvant, develop experimental autoimmune uveitis (EAU). Lymph node cells and peripheral lymphocytes from immunized animals manifested significant cellular immune responses measured by the lymphocyte culturing technique. Cyclosporine, a drug with specific anti-T-activity, has been found to be exceptionally effective in protecting rats with EAU, and suppressor cells potentially play a role in this protective mechanism. As well, the inducer cell T-cell fraction in the lymph node appears to be most susceptible to cyclosporine therapy. Attempts at local immunosuppressive therapy in order to prevent EAU have begun. The use of topical CsA has been used to evaluate its effectiveness in EAU. Additionally, newer cyclosporines, particularly D&G, have been evaluated in this model, with their efficacy compared to that of cyclosporine A.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00115-05 CB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Cyclosporine Therapy in Uveitis

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

PI:	Robert B. Nussenblatt	M.D.	Head, Section on Clinical Ophthalmic Immunology	CB, NEI
Others:	Alan G. Palestine	M.D.	Staff Ophthalmologist	CB, NEI
	Garth Stevens, Jr.	M.D.	Senior Staff Fellow	CB, NEI
	Leslie S. Fujikawa	M.D.	Senior Staff Fellow	CB, NEI
	Francois Roberge	M.D.	Guest Researcher	CB, NEI
	Igal Gery	Ph.D.	Visiting Scientist	LVR, NEI

COOPERATING UNITS *(if any)*

National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases Section (Howard Austin, III, M.D.)

LAB/BRANCH

Clinical Branch

SECTION

Section on Ophthalmic Immunology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
2.50	2.00	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.)*

Cyclosporine, an endecapeptide fungal product with specific anti-T-cell characteristics, will be administered to patients with sight-threatening ocular inflammatory disease of non-infectious origin who have failed on either corticosteroid or cytotoxic agent therapy. This will be done to test cyclosporine's efficacy in the treatment of uveitis. Within the context of these ongoing studies, the effect of hydergine on reversing cyclosporine induced nephrotoxicity is being evaluated in a randomized, masked, cross-over study. Additionally, selected patients whose uveitis is well controlled on cyclosporine for one year or more are undergoing kidney biopsies to evaluate the long term effects of this agent.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00117-05 CB

PERIOD COVERED
October 1, 1984 to September 30, 1985

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

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

PI:	Jon N. Currie	M.D.	Acting Head, Section on Neuro-ophthalmology	CB, NEI
Others:	David G. Cogan	M.D.	Head, Section on Neuro-ophthalmology	CB, NEI
	Georgia A. Chrousos	M.D.	Guest Worker	CB, NEI
	Victor Matsuo	Ph.D.	Staff Fellow	CB, NEI
	James R. Carl	M.D.	Senior Staff Fellow	LSR, NEI

COOPERATING UNITS *(if any)*
None

LAB/BRANCH
Clinical Branch

SECTION
Section on Neuro-ophthalmology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.7	0.6	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.)*

Oscillopsia and reduced visual acuity due to retinal image slip caused by acquired nystagmus, and in particular by downbeating nystagmus, can be temporarily reduced or eliminated by a single dose of clonazepam and a sustained beneficial effect can be obtained with daily use of clonazepam.

Ocular motor abnormalities in Kallman's syndrome suggest that dysfunction of the cerebellar vermis may also be part of this syndrome. Eye movement abnormalities in multisystem atrophy (Shy-Drager Syndrome) and olivopontocerebellar atrophy were studied to provide diagnostic and prognostic information. Studies of eye movements in patients with familial Alzheimer's disease and their first order (at risk) relatives attempt to provide additional diagnostic, prognostic and therapeutic monitoring information.

Saccadic velocities have been shown to be a sensitive indicator of benzodiazepine drug effects in man. Caffeine acts as a benzodiazepine antagonist for the degredation of saccadic velocities but not for cognitive function, suggesting different benzodiazepine receptor functions for these two parameters.

Carbamazepine induced downbeating nystagmus in two patients without craniocervical abnormalities and this resolved when carbamazepine levels were reduced.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 EY 00121-05 CB

October 1, 1984 to September 30, 1985

Spatial Contrast Sensitivity Studies in Retinal and Neuro-ophthalmol. Disease

PI:	Kent E. Higgins	Ph.D.	Expert	CB, NEI
Others:	F. M. de Monasterio	M.D., D.Sc.	Chief, SVP	CB, NEI
	Rafael C. Caruso	M.D.	Expert	CB, NEI
	Monique S. Roy	M.D.	Visiting Scientist	CB, NEI

Clinical Branch

Section on Visual Processing

NEI, NIH, Bethesda, Maryland 20892

0.80 0.50 0.30

x (a) Human subjects

x (a1) Minors

x (a2) Interviews

Spatial contrast sensitivity was used to assess losses or changes in overall visual resolution in patients having a variety of toxic, inflammatory, degenerative, or congenital retinal and neuro-ophthalmological disorders of the visual system. A criterion-free forced-choice psychophysical procedure was used, since this method was previously shown to minimize spurious changes in sensitivity was repeated testing. During this past year, the use of technique was broadened to include the evaluation of vision in cataractous patients and to evaluate a hypothesis concerning the relationship between blood sugar level and contrast sensitivity in diabetic patients.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 EY 00122-05 CB

October 1, 1984 to September 30, 1985

Anatomical Studies of the Visual System of Primates

PI:	Francisco M. de Monasterio	M.D., D.Sc.	Chief, SVP	CB, NEI
Others:	Stanley J. Schein	M.D., Ph.D.	Guest Worker	Mass Eye & Ear
	Edna P. McCrane	B.S.	Biologist	CB, NEI

Howe Laboratory of Neuro-ophthalmology, Massachusettes Eye and Ear Infirmary, Harvard Medical School

Clinical Branch

Section on Visual Processing

NEI, NIH, Bethesda, Maryland 20892

0.60 0.25 0.35

We have examined the dependence of blue cone denisty on retinal eccentricity in the central square region of about 10 degrees on the side. From these density counts three dimensional plots are obtained to assess the shape and degree of circular symmetry of the blue-cone peak density at different meridia.

The pattern of cytochrome-oxidase (CO) reactivity in the striate cortex of macaques that had chronic unilateral enucleation exhibits "spots" in the upper layers (II and III) and ocular-dominance "stripes" in layer IV of the cortex. The same pattern is obtained with the metabolic marker 2-Deoxyglucose (2DG) in macaques in which one eye is patched or occluded. It has been assumed that the same 2DG-pattern was also to be obtained in (acutely or chronically) unilaterally enucleated macaques. However, we have found a dissociation between the CO and 2DG patterns in such animals, since with the 2DG method the acutely enucleated monkeys show "stripes" in the upper layers as well as in layer IV of cortex. These results indicate that the maintained discharge from the non-seeing eye can influence the uptake of 2DG by cells located in the seeing cortical column.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00133-02 CB

PERIOD COVERED
October 1, 1984 to September 30, 1985

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Virologic and Immunopathologic Aspects of Eye Diseases

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

PI:	John J. Hooks	Ph.D.	Microbiologist	CB, NEI
Others:	Caroline Percopo	A.B.	Biologist	CB, NEI
	Yotanna Dalavanga	M.D.	Visiting Fellow	CB, NEI
	Garth Stevens, Jr.	M.D.	Senior Staff Fellow	CB, NEI
	Muriel I. Kaiser-Kupfer	M.D.	Head, Section on Ophthalmic Gen. & Ped. Ophthal.	CB, NEI
	Barbara Detrick-Hooks	Ph.D.	Expert	

COOPERATING UNITS *(if any)* Johns Hopkins University, Baltimore, Maryland (Judith Whittum, Ph.D.); Duke University, Durham, North Carolina (Barton F. Haynes, M.D.); Paris, France (Laurence Boumsell, M.D.); Paris, France (Alain Bernard, M.D.); Ioannina, Greece (Haralampos Moutsopoulos, M.D.)

LAB/BRANCH
Clinical Branch

SECTION
Section on Ophthalmic Immunology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
3.10	2.35	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.)*

Virologic and immunopathologic aspects of eye diseases are being studied by the identification of immunoregulatory systems in vision and ocular disease and by the evaluation of the involvement of viruses in the etiology and pathogenesis of eye diseases.

Regulatory mechanisms in disease are being investigated by concentrating on the interactions among lymphokines (interferon (IFN), interleukin 2), cell surface proteins (HLA-DR, Ia) and selected cells within the eye (retinal pigment epithelial (RPE) cell, photoreceptors, endothelial cells). These studies have identified alterations in the IFN system and class II antigens in retinal degenerations, inflammatory eye diseases and in selected immunologically mediated diseases (Acquired Immunodeficiency Syndrome (AIDS), autoimmunity). Studies are in progress to develop monoclonal antibodies to identify retinal cells (RPE). Since the RPE cell is an important regulatory cell in the retina, the interactions among lymphokines, class II antigens and RPE cell function are being evaluated.

The role of viruses in the etiology and pathogenesis of eye diseases in man and animals is being studied. Attempts to identify viruses in tissues from patients with uveitis and acute retinal necrosis are in progress.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00144-04 CB

PERIOD COVERED

October 1, 1984 to September 30, 1985

TITLE OF PROJECT (Do not exceed the space provided. Do not use abbreviations unless they are commonly understood.)

Clinical Electrophysiology of the Visual System

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

PI: Rafael C. Caruso M.D. Expert CB, NEI

OTHER PERSONNEL (Name, title)

None

LABORATORY

Clinical Branch

BRANCH

Section on Visual Processing

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.55	0.55	0.0

CHECK APPROPRIATE BOX(ES)

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

(a1) Minors

(a2) Interviews

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

Visual evoked responses are recorded in normal volunteers and in patients with lesions of the retina, optic nerves, optic chiasm, optic radiations and visual cortex. Both pattern stimuli and unstructured stimuli are used. The recordings are used for diagnostic purposes and to provide an objective assessment of visual function in these conditions. These data are correlated with the results of phsychophysical tests of visual function.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00160-03 CB

PERIOD COVERED
October 1, 1984 to September 30, 1985

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Visual Inattention After Posterior Cerebral Hemisphere Lesions

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

PI:	Jon N. Currie	M.D.	Acting Head, Section on Neuro-ophthalmology	CB, NEI
Others:	David G. Cogan	M.D.	Head, Section on Neuro-ophthalmology	CB, NEI
	Georgia A. Chrousos	M.D.	Guest Worker	CB, NEI
	Linda R. Dagi	M.D.	Staff Fellow	CB, NEI
	Victor Matsuo	Ph.D.	Staff Fellow	CB, NEI

COOPERATING UNITS *(if any)*
Laboratory of Sensory Motor Research, NEI (D. L. Robinson, S. E. Petersen, and M. E. Goldberg); Clinical Neurosurgery Section, NINCDS (G. Di Chiro)

LAB/BRANCH
Clinical Branch

SECTION
Section on Neuro-ophthalmology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.2	1.0	0.2

CHECK APPROPRIATE BOX(ES)

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

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

A sub group of dyslexic patients with square wave jerks present during fixation and reading was identified and both reading ability and square wave intrusions were markedly improved with methylphenidate.

Directionally cued visual behavior is impaired in the visual field contralateral to parietal lesions in humans, but diffusely cued visual tasks are impaired in both visual fields. Similar deficits are found when lesions are made in area 7 or the lateral pulvinar of the macaque. Pursuit function was studied in patients with parietal and frontal lobe lesions, schizophrenia and Alzheimer's disease, and a comparison was made with slow phase velocity of OKN. The frequency of fixational square wave jerks was also studied in the above patients and also in patients with hypothalamic and chiasmal tumors.

Cortical visual loss occurred as a temporary side effect in four patients receiving high dose intravenous chemotherapy for lymphoma or leukemia. Magnetic resonance scanning showed good anatomic correlation, with occipital lobe edema.

Positron emission scanning (PET) was used to correlate visual functions with glucose utilization in different anatomical areas of the brain. This included patients with homonymous hemianopias, bilateral optic nerve transection and albinism.

The possible contribution of extrageniculostriate pathways to visual processing following lesions of the geniculostraite pathway was studied in patients with lesions of optic chiasm, primary visual cortex or optic radiations.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00161-03 CB

PERIOD COVERED
October 1, 1984 to September 30, 1985

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

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

PI:	Jon N. Currie	M.D.	Acting Head, Section on Neuro-ophthalmology	CB, NEI
Others:	Georgia A. Chrousos	M.D.	Guest Worker	CB, NEI
	David G. Cogan	M.D.	Head, Section on Neuro-ophthalmology	CB, NEI
	Victor Matsuo	Ph.D.	Staff Fellow	CB, NEI

COOPERATING UNITS *(if any)*
None

LAB/BRANCH
Clinical Branch

SECTION
Section on Neuro-ophthalmology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.5	0.4	0.1

CHECK APPROPRIATE BOX(ES)

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

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

A single dose of clonazepam may be used to reduce the intensity of congenital nystagmus or to eliminate it altogether for a short period of time, allowing assessment of underlying visual acuity without visual impairment due to retinal image slip. An oculographic study in spasmus nutans shows that head turning transiently dampens the nystagmus. The nystagmus present in rod monochromaticity showed a predominantly pendular wave form.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00162-03 CB

PERIOD COVERED

October 1, 1984 to September 30, 1985

TITLE OF PROJECT

Vitreous Fluorophotometry

PRINCIPAL INVESTIGATOR

PI: Monique Roy M. D. Visiting Scientist CB, NEI

COOPERATING UNITS

None

LAB/BRANCH

Clinical Branch

SECTION

Section on Ophthalmic Genetics and Pediatric Ophthalmology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS PROFESSIONAL OTHER

CHECK APPROPRIATE BOX(ES)

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

(a1) Minors

(a2) Interviews

SUMMARY OF WORK

Vitreous fluorophotometry will be performed in patients with diabetes mellitus without retinopathy, patients with diabetes mellitus with nonproliferative retinopathy, and normal volunteer subjects, age-, number-, and sex-matched to the patients. The amount of fluorescein leakage into the vitreous of patients will be compared to that of the normal subjects. Correlations with other features of diabetes, such as the quality of diabetic control, the existence of subclinical neuropathy and nephropathy, and others will be sought.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00163-03 CB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

NIH Interinstitute Medical Genetics Program: The Genetics Clinic

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

PI:	Muriel I. Kaiser-Kupfer	M.D.	Head, Section on Ophthalmic Genetics and Pediatric Ophthalmology	CB, NEI
Others:	Paul Edwards	M.D.	Visiting Fellow	CB, NEI
	Lessie McCain	R.N.	Clinical Technician	CB, NEI
	Linda Wang	B.S.	Health Technician (Ophth.)	CB, NEI

COOPERATING UNITS (if any)

LAB/BRANCH

Clinical Branch

SECTION

Section on Ophthalmic Genetics and Pediatric Ophthalmology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
.4	.2	.2

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 Interinstitute Medical Genetics Program and the Genetics Clinic, supported by the Clinical Center, offer a multidisciplinary approach to patients with genetic disease (Z01 CP 05139-04 CEB). Involved in the program are researchers from all Institutes. Patients evaluated in the clinic represent a broad spectrum of genetic disease. During the last year, approximately 423 individuals were seen, representing approximately 100 different disease categories. Due to the high frequency of ocular involvement in many of the cases, almost all the patients were evaluated by Clinical Branch staff or were discussed in consultation. The Clinic serves as a source of interesting case material concerning patients with inherited or developmental abnormalities of the visual system.

In addition to the Genetics Clinic, patients are seen for genetic consultation at the Maryland School for the Blind. This experience has resulted the recruitment of patients into Clinical Branch protocols.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 EY 00172-03 CB

October 1, 1984 to September 30, 1985

Senile Macular Degeneration

PI:	Muriel I. Kaiser-Kupfer	M.D.	Head, Section on Ophthalmic Genetics	CB, NEI
Others:	Carl Kupfer	M.D.	Director	NEI
	Monique Roy	M.D.	Visiting Scientist	CB, NEI

None

Clinical Branch

Section on Ophthalmic Genetics and Pediatric Ophthalmology

NEI, NIH, Bethesda, Maryland 20892

x (a) Human Subjects ☐ (b) Human Tissues ☐ (c) Neither

☐ (a1) Minors

☐ (a2) Interviews

This study will determine if patients with severe visual loss because of senile macular degeneration in one eye and with good vision in the second eye can be protected from severe visual loss in the good eye by the administration of vitamin E and vitamin C when exposure of the retina to light below 500 nanometers is diminished. The recruited patients will be randomly assigned either to a treated or an untreated control group and examined at four-month intervals. Follow-up will continue for five years, unless an early beneficial or detrimental effect causes the study to be terminated in less than five years.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 EY 00173-03 CB

PERIOD COVERED

October 1, 1984 to September 30, 1985

TITLE OF PROJECT

Neuropharmacology of the Human Electroretinogram

PI:	Francisco M. de Monasterio	M.D., D.Sc.	Chief, SVP	CB, NEI
Others:	Myles J. Jaffe	O.D.	Staff Fellow	CB, NEI
	Paul Levinson	M.D.	Clinical Associate	NHLBI
	Dan Hommer	M.D.	Clinical Associate	NIMH
	Roger Rittmaster	M.D.	Clinical Associate	NICHHD
	Dan Weinberger	M.D.	Clinical Associate	NINCDS

COOPERATING UNITS (if any)

Endocrine and Hypertension Section, NHLBI
NIMH, NICHHD, NINCDS

LABORATORY AND BRANCH

Clinical Branch

SECTION AND UNIT

Section on Visual Processing

LOCATION (Building, Room No., City, State)

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS: 0.25 | PROFESSIONAL: 0.25 | OTHER: 0.0

CHECK APPROPRIATE BOX(ES)

x (A) Human Subjects (B) Human Tissues (C) Neither

(A1) N/A

(A2) In progress

(A3) To be submitted

ABSTRACT

Multiple neuromodulators are known to exist within the cell bodies of the retina's inner nuclear layer; some of these have been shown to be released by flashes of light. The function of these modulators following their release is currently unknown. To study this, we have altered the release of these substances pharmacologically with either antagonists or agonists. Baseline electroretinograms (ERG) were compared with those influenced by the administered drug. The effects of several drugs were studied: (1) Patients with Parkinson's disease were taken off all medication for 24-48 hours as part of another protocol; and baseline ERGs were then obtained. A second ERG was obtained following 2 hours of continuous L-Dopa infusion. Comparison of these ERGs suggest that application of exogenous dopamine in these patients increases the amplitude of the rod and cone b wave. (2) Other patients with Hemi-Parkinson's disease (and never on dopaminergic drugs) had their ERGs evaluated bilaterally: There were no obvious differences between the eye ipsilateral to the Parkinsonian tremors and the contralateral eye.
(3) Patients with schizophrenia had placebo in place of haloperidol as part of another protocol; these patients remained "drug free" for at least two weeks. By comparison to age and sex matched norms, the implicit time of the "blue" cone b-wave was increased. This was confirmed in a second, independent study.
(4) In normals, the specific dopamine antagonist metoclopramide was evaluated following an IV bolus administration. Cone a wave and b wave amplitudes were reduced under both dark and light adapted conditions. This reduction was more pronounced under dark-adapted conditions, implying that the neuro-modulatory function of dopamine is more marked in the dark.

PHS 6348 (Rev. 6-82)

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 EY 00174-03 CB

PERIOD COVERED

October 1, 1984 to September 30, 1985

TITLE

Simulation of Visual Impairments in Normal Subjects

PI:	Kent E. Higgins	Ph.D.	Expert	CB, NEI
Others:	Rafael C. Caruso	M.D.	Expert	CB, NEI

None

Clinical Branch

Section on Visual Processing

NEI, NIH, Bethesda, Maryland 20892

0.10 0.10 0.0

x

The relationship between spatial contrast sensitivity and visual field loss was examined using an artificial scotoma technique. Central-field contrast sensitivity was measured in normal subjects both with and without artificial, central scotomata of varying sizes and using a forced-choice psychophysical method. Previously, it was found that the type of contrast sensitivity loss observed with 5 degree grating field depended both on the size of the artifical scotoma and on temporal factors associated with grating presentation. Small artificial scotoma produced a predominantly high spatial frequency loss. Larger scotomata produced a middle and low spatial frequency loss which was acentuated by turning grating contrast on and off abruptly as opposed to gradually. Research during this past year, has shown that similar findings are obtained when grating field size and artificial scotoma size are increased by a factor of approximately three.

FORM

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00175-03 CB

October 1, 1984 to September 30, 1985

Normative Studies of Spatial Contrast Sensitivity

PI:	Kent E. Higgins	Ph.D.	Expert	CB, NEI
Others:	F. M. de Monasterio	M.D., D.Sc.	Chief, SVP	CB, NEI
	Myles J. Jaffe	O.D.	Staff Fellow	CB, NEI
	Rafael C. Caruso	M.D.	Expert	CB, NEI
	Patricia A. Mercer	B.A	Clinical Research Technician (Ophth)	CB, NEI

None

Clinical Branch

Section on Visual Processing

NEI, NIH, Bethesda, Maryland 20892

0.82 0.37 0.45

x

x

x

Age-referenced test and retest normative data were collected for a new forced-choice spatial contrast sensitivity test system that was designed to permit greater flexibility in selection of mean luminance level and field size for patient testing and 2) reduce testing time by approximately 30%. Subjects ranged in age from 5 to 70 years.

Approximately 1/2 of the required subjects completed testing during the past year. Preliminary results indicate that the new system is as reliable as the previous system, while requiring only 2/3 the testing time of the previous system.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00184 -03 CB

PERIOD COVERED
October 1, 1984 to September 30, 1985

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
T-Cell Lines and Clones in Uveitis

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

PI:	Rachel Caspi	Ph.D.	Visiting Fellow	CB, NEI
Others:	Robert B. Nussenblatt	M.D.	Head, Section on Clinical Ophthalmic Immunology	CB, NEI
	Magda El-Saied	M.B.	Visiting Associate	CB, NEI
	Consuelo Muellenberg-Coulombre		Chemist	CB, NEI
	Alan G. Palestine	M.D.	Staff Ophthalmologist	CB, NEI

COOPERATING UNITS *(if any)*

LAB BRANCH
Clinical Branch

SECTION
Section on Ophthalmic Immunology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20205

TOTAL MAN YEARS	PROFESSIONAL	OTHER
3.07	1.07	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.)*

Long-term T-cell lines and T-cell clones are maintained in vitro from both peripheral blood and ocular fluids of humans and animals. The goal of these studies will be to identify the immunoreactive cells and mediators involved in the intraocular inflammatory process.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00187-02 CB

PERIOD COVERED
October 1, 1984 to September 30, 1985

TITLE OF PROJECT *(80 characters or less Title must fit on one line between the borders)*
The Effects of Corneal Contact Lenses on the Cornea

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

PI:	Manuel B. Datiles	M.D.	Visiting Scientist	CB, NEI
Others:	Carl Kupfer	M.D.	Director	NEI
	Lessie McCain	R.N.	Clinical Technician	CB, NEI
	Muriel I. Kaiser-Kupfer	M.D.	Head, Section on Ophthalmic Genetics and Pediatric Ophthalmology	CB, NEI
	Linda Wang	B.S.	Health Technician (Ophth)	CB, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Branch

SECTION
Section on Ophthalmic Genetics and Pediatric Ophthalmology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.70	0.35	0.35

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)*

Short, as well as long-term effects of contact lens wear on the cornea are being investigated. Changes in corneal curvature, changes in corneal epithelial morphology and changes in corneal endothelial cell morphology are being studied by specular microscopy.

These data will help us understand the dynamics involved in the interaction between a contact lens and the cornea, the risks involved to corneal tissues, and how a systemic or local disorder may increase these risks.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00188-02 CB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Documentation and Monitoring of Opacities in the Human Lens

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

PI:	Manuel B. Datiles	M.D.	Visiting Scientist	CB, NEI
Others:	Carl Kupfer	M.D.	Director	NEI
	Robert Sperduto	M.D.	Epidemiologist	OBE, NEI
	Peter Kador	Ph.D.	Chemist	LVR, NEI
	Lessie McCain	R.N.	Clinical Technician	CB, NEI
	Paul Edwards	M.D.	Visiting Fellow	CB, NEI

COOPERATING UNITS *(if any)*

Benes Trus	Ph.D.	Imaging Processing Laboratory	DCRT, NIH

LAB/BRANCH

Clinical Branch

SECTION

Section on Ophthalmic Genetics and Pediatric Ophthalmology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.85	0.75	0.10

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

We are in the process of developing the means to monitor and document opacities in the human lens using different systems. We have recently acquired a Scheimpflug camera, which is presently the best means of documenting cataracts. However, we are exploring other means such as ultrasonography, specular microscopy, nuclear magnetic resonance, Kawara photography and Laser imaging. We are also exploring other methods of documenting how opacities in the lens affect vision, such as glare testing, contrast sensitivity measurements, Laser Interferometry and Potential Acuity Meter testing.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00202-01 CB

PERIOD COVERED
October 1, 1984 to September 30, 1985

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Randomized Double-Masked Study of Cyclosporine in Treating Endogenous Uveitis

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

PI:	Robert B. Nussenblatt	M.D.	Head, Section on Clinical Ophthalmic Immunology	CB, NEI
Others:	Alan G. Palestine	M.D.	Staff Ophthalmologist	CB, NEI
	Garth Stevens, Jr.	M.D.	Senior Staff Fellow	CB, NEI
	Leslie S. Fujikawa	M.D.	Senior Staff Fellow	CB, NEI
	Chi-Chao Chan	M.D.	Staff Ophthalmologist	CB, NEI
	William J. Dinning	M.D.	Visiting Scientist	CB, NEI

COOPERATING UNITS *(if any)*
National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases Section (Howard Austin, III, M.D.)

LAB/BRANCH
Clinical Branch

SECTION
Section on Ophthalmic Immunology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
2.50	2.00	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.)*

Cyclosporine's efficacy in the treatment of severe endogenous uveitis is being evaluated in this randomized, double masked study. The study will evaluate the effectiveness of cyclosporine therapy to that of systemic corticosteroid administration. Patients meeting the entry requirements will be randomized to either cyclosporine or corticosteroid therapy. Patients are evaluated at three months in order to determine whether they are therapeutic "successes" or not. If not, the patients are then treated with the alternate medication.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00203-01 CB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Lymphocyte Migration in Experimental Autoimmune Uveitis

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

PI:	Alan G. Palestine	M.D.	Staff Ophthalmologist	CB, NEI
Others:	Robert B. Nussenblatt	M.D.	Head, Section on Clinical Ophthalmic Immunology	CB, NEI
	Igal Gery	Ph.D.	Visiting Scientist	LVR, NEI
	Cathy McAllister	Ph.D.	Extramural Fellow	LVR, NEI
	Barbara Vistica	B.A.	Microbiologist	LVR, NEI
	Myung Kim	M.D.	Guest Researcher	CB, NEI

COOPERATING UNITS *(if any)*

Nuclear Medicine, Clinical Center (Andrew Keenan, M.D.); Blood Bank, Clinical Center (Richard Davy, M.D.); Blood Bank, Clinical Center (Charles Carter)

LAB/BRANCH

Clinical Branch

SECTION

Section on Ophthalmic Immunology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
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.)*

Experimental autoimmune uveitis (EAU) is induced by immunization of rats and other experimental animals with S-antigen (a soluble antigen from the retina) is being investigated in this laboratory as a model of human intra-ocular inflammation. This experimental inflammation can be transferred from donor rats to naive recipients using lymphocytes harvested from the spleen or lymph nodes. Following harvesting of the cells from the donors and three days in culture with stimulating antigen, the cells are injected into the intra-peritoneal cavity and five to seven days later the recipient rats develop EAU. The mechanism of transfer of disease is unclear. This work has used radioactively labeled lymphocytes to determine the fate of these lymphocytes after injection into the peritoneal cavity and during the process of the development of uveitis. The goal of this project is to understand the initiating mechanisms of inflammation in the hope that these mechanisms can be extended and applied to human inflammations. Thus far we have determined that only a small percentage of the lymphocytes injected into the peritoneal cavity actually reach the eye during the induction of EAU. Of 100 million cells transferred into the peritoneal cavity, approximately 5,000 reach the eye. Many more reach the spleen, liver and thymus however. Further studies of the time course and type of cell reaching the inflamed eye are in progress with the goal of understanding the relationship between donor and host lymphocytes in EAU.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00204-01 CB

PERIOD COVERED
October 1, 1984 to September 30, 1985

TITLE OF PROJECT *(80 characters or less Title must fit on one line between the borders.)*
Vascular Endothelium & Class II Antigens in Ocular Inflammatory Disease

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

PI:	Leslie S. Fujikawa	M.D.	Senior Staff Fellow	CB, NEI
Others:	Chi-Chao Chan	M.D.	Staff Ophthalmologist	CB, NEI
	Igal Gery	Ph.D.	Visiting Scientist	LVR, NEI
	Barbara Detrick	Ph.D.	Expert	LVR, NEI
	John J. Hooks	Ph.D.	Microbiologist	CB, NEI
	Robert B. Nussenblatt	M.D.	Head, Section on Clinical Ophthalmic Immunology	CB, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Branch

SECTION
Section on Ophthalmic Immunology

INSTITUTE AND LOCATION
NEI, 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)*

Activation of the vascular endothelium in the retina was studied in the model of experimental autoimmune uveitis in the rat (retinal S antigen model). Immunohistochemical techniques were used to characterize the expression of fibronectin, Ia and Ie antigens (class II antigens). Results showed that fibronectin appears several days prior to the cellular infiltrate, Ie antigen appears 2 days prior to infiltration, and Ia appears at the time of cellular infiltration. This indicates that the vascular endothelium, which comprises retinal inflammation to occur, is activated prior to the cellular infiltration, any may therefore play a role in the local recruitment and development of uveitis in this model.

Class II antigens are also expressed on other cell types during this ocular inflammation. This includes cells of the cornea, sclera, and retinal pigment epithelium.

In vitro induction of class II antigens was demonstrated on cells of the cornea (human, rat), conjunctiva (rat), and sclera (rat) by the addition of gamma interferon-containing supernatants. Preliminary results show that Ia-positive corneal cells in culture may be inhibitory in antigen-presentation to T cells. Studies on retinal vascular endothelium in culture are currently being pursued.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00205-01 CB

PERIOD COVERED
October 1, 1984 to September 30, 1985

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Human T-Cell Leukemia/Lymphotropic Virus Type III in Ocular Fluids & Tissues

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

PI:	Leslie S. Fujikawa	M.D.	Senior Staff Fellow	CB, NEI
Others:	Alan G. Palestine	M.D.	Staff Ophthalmologist	CB, NEI
	Robert B. Nussenblatt	M.D.	Head, Section on Clinical Ophthalmic Immunology	CB, NEI

COOPERATING UNITS *(if any)* Laboratory of Tumor Cell Biology, National Cancer Institute (S. Zaki Salahuddin, M.D.); Laboratory of Cellular and Molecular Biology, National Cancer Institute (Dharam Ablashi, M.D.); Department of Critical Care Medicine, Clinical Center (Henry Masur, M.D.); Laboratory of Tumor Cell Biology, National Cancer Institute (Robert C. Gallo, M.D.)

LAB/BRANCH
Clinical Branch

SECTION
Section on Ophthalmic Immunology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20205

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.)*

HTLV-III was studied in ocular fluids and cells in order to characterize its possible involvement in ophthalmic disease in AIDS and possible transmissibility through ocular fluids.

a. HTLV-III was isolated from the tear fluid of patients with AIDS by using Schirmer's filter paper strips and infection of lymphocytes plus retransmission to other lymphocytes.

b. Studies indicate that conjunctival epithelial cells from AIDS patients contain HTLV-III and may therefore serve as a reservoir for the virus.

c. Further studies in progress suggest more widespread presence of HTLV-III in ocular fluids.

d. Precautions are recommended during ophthalmic examination in order to prevent any possible spread of the virus by this route. Although this has not been documented to occur, the Centers for Disease Control has issued such precautions. Morbid. Mortal. Weekly Report 34:533-534, 1985.

Fujikawa, L.S., Salahuddin, S.Z., Palestine, A.G., Masur, H., Nussenblatt, R.B., Gallo, R.C.: Isolation of Human T-Cell Leukemia/Lymphotropic Virus Type III (HLTV-III) from the Tears of a Patient with the Acquired Immunodeficiency Syndrome (AIDS). Lancet ii:529-530, 1985.

Fujikawa, L.S., Salahuddin, S.Z., Ablashi, D., Palestine, A.G., Masur, H., Nussenblatt, R.B., Gallo, R.C.: Human T-Cell Leukemia/Lymphotropic Virus Type III in the Conjunctival Epithelium of a Patient with AIDS. Amer. J. Ophthal. 1985 (in press).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00206-01 CB

PERIOD COVERED
October 1, 1984 to September 30, 1985

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
The Role of Fibronectin in Wound Healing in the Eye

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

PI:	Leslie S. Fujikawa	M.D.	Senior Staff Fellow	CB, NEI
Others:	Robert B. Nussenblatt	M.D.	Head, Section on Clinical Ophthalmic Immunology	CB, NEI
	Manuel B. Datiles	M.D.	Visiting Scientist	CB, NEI
	Patricia F. Tenn	M.D.	Guest Researcher	CB, NEI
	Roberta E. Lee	M.D.	Guest Researcher	CB, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Branch

SECTION
Section on Ophthalmic Immunology

INSTITUTE AND LOCATION
NEI, 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 role of fibronectin in corneal wound healing was studied both in man and in experimental animals. Studies were carried out in order to characterize the possible effect of fibronectin on facilitating wound healing of the epithelium.

a. Alkali burn model in rabbits. During the healing of an alkali burn, the surface epithelium does not heal normally, and it was found that there was less fibronectin and other basement membrane components, such as laminin, on the wounded surface. Topical fibronectin was found to allow the epithelial layer to remain intact longer during the healing of this wound, suggesting that exogenous fibronectin added in the form of an eyedrop may facilitate corneal wound healing. Experiments with other components, such as laminin, have also been done and are being analyzed.

b. Because of the positive effect of fibronectin in experimental systems involving corneal epithelial wound healing, a clinical protocol was initiated in collaboration with the Massachusetts Eye & Ear Infirmary. This study is a randomized clinical trial comparing fibronectin eyedrops prepared from the patient's own plasma to placebo (serum albumin).

c. Biopsy specimens from patients have been studied for the presence of fibronectin in healing wounds. Fibronectin is present in retrocorneal fibrous membrane, as well as in certain conjunctival and corneal inflammatory conditions. Type III collagen appears to be associated with fibronectin in wounds involving healing fibroblasts or endothelium.

d. Additional current laboratory studies are directed at mechanisms of corneal cell attachment mediated by fibronectin.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00207-01 CB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Immunopathological Studies in Ocular Inflammatory Diseases

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

PI: Chi-Chao Chan M.D. Staff Ophthalmologist CB, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Clinical Branch

SECTION

Section on Ophthalmic Immunology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20205

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.)*

During the past year we have evaluated the identity and topographic localization of immunocompetent cells in patients with different stages of uveitis and in Lewis rats with experimental autoimmune uveitis by immunopathological study (immunoperoxidase technique). The data demonstrated that the predominant infiltrating cells in the eye was mainly T-lymphocytes with the T-helper/inducer cells in the early stage and a relative increase of T-suppressor/cytotoxic cells in the later stage. We have also observed the expression of class II antigens on some ocular tissue (vascular endothelium, retinal pigmented epithelium and fibroblast) prior to and during the development of the disease, and the consequence of inflammation: destruction of photoreceptors, formation of cyclitic or preretinal membrane and gliosis. These observations may reflect the kinetics and regulation of the ocular autoimmune process and help us to understand the pathogenesis of these ocular diseases.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00208-01 CB

PERIOD COVERED
October 1, 1984 to September 30, 1985

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Study of Ocular Glial Cells Involvement In Uveitis

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

PI:	Francois Roberge	M.D.	Guest Researcher	CB, NEI
Others:	Robert B. Nussenblatt	M.D.	Head, Section on Clinical Ophthalmic Immunology	CB, NEI
	Chi-Chao Chan	M.D.	Staff Ophthalmologist	CB, NEI
	Rachel Caspi	Ph.D.	Visiting Fellow	CB, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Clinical Branch

SECTION
Section on Ophthalmic Immunology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20205

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.)*

Muller cells from adult rat retina are purified and maintained in culture. Culture medium is defined. Interactions with inflammatory mononuclear cells are studied.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00209-01 CB

PERIOD COVERED
October 1, 1984 to September 30, 1985

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

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

PI:	Jon N. Currie	M.D.	Acting Head, Section on Neuro-ophthalmology	CB, NEI
Others:	Linda R. Dagi	M.D.	Staff Fellow	CB, NEI

COOPERATING UNITS *(if any)*
None

LAB/BRANCH
Clinical Branch

SECTION
Section on Neuro-ophthalmology

INSTITUTE AND LOCATION
NEI, NIH, 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.)*

Normative values were derived for the effects of different doses of dilute pilocarpine on pupil diameter, and these were used to study denervation supersensitivity in both pre- and postganglionic parasympathetic lesions.

Patients with Shy Drager syndrome and alternating Horner's syndrome were studied to determine the possible mechanisms for this abnormality. A study of the effect of light and darkness on pupil diameter in Horner's syndrome revealed that anisocoria is not necessarily greater in darkness, as had been previously thought.

Studies were made on the effects of aging on pupil size and parasympathetic and sympathetic reactivity.

The phenomenon of paradoxical pupillary constriction in darkness was studied in three patients with rod monochromatism.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00210-01 CB

PERIOD COVERED
October 1, 1984 to September 30, 1985

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Model Program for Collaboration Between Cataract Surgeons and Ophthalmic Researchers

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

PI:	Manuel B. Datiles	M.D.	Visiting Scientist	CB, NEI
Others:	Carl Kupfer	M.D.	Director	NEI
	Samuel Zigler	Ph.D.	Chemist	LVR, NEI
	Paul Russell	Ph.D.	Chemist	LVR, NEI
	Peter Kador	Ph.D.	Chemist	LVR, NEI
	Paul Edwards	M.D.	Visiting Fellow	CB, NEI

COOPERATING UNITS *(if any)*

Consultant - Jin H. Kinoshita	Ph.D. Scientific Director	NEI

LAB/BRANCH
Clinical Branch

SECTION
Section on Ophthalmic Genetics and Pediatric Ophthalmology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.95	0.65	0.30

CHECK APPROPRIATE BOX(ES)

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

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

There is presently an extreme dearth of human cataract material because of an abrupt shift of cataract surgical technique from intracapsular (intact lens) to extracapsular (fragmented lens), primarily because of advent of the use of the intraocular lens. We are exploring ways by which fragmented lens materials can be maximally used in cataract biochemical research through close collaboration between cataract surgeons and biochemists and modification of techniques by both groups.

ANNUAL REPORT
NATIONAL EYE INSTITUTE
October 1, 1984 - September 30, 1985

REPORT OF THE CHIEF, LABORATORY OF VISION RESEARCH

Gerald J. Chader, Ph.D.

Since the formation of the National Eye Institute, the mission of the Laboratory of Vision Research has been to study normal and pathological processes in ocular tissues with the primary emphasis on lens and retina. Using multidisciplinary approaches, LVR investigators elucidate and define important pathways critical to the functioning of the tissues. In conjunction with this, disease processes are studied in an attempt to understand the dysfunction. Most importantly, attempts are made to correct or alleviate the abnormal condition. In our laboratory, this last year has seen significant advances in pharmacological studies on diabetes and the application of molecular biological techniques to the study of an important retinal protein involved in the visual process.

Following are some highlights of the research conducted by members of the LVR during the year:

1. Section on Lens and Cataract: Under the leadership of Dr. Jin Kinoshita, this group is the single most productive group in the area of lens research. Dr. Peter Kador has continued his studies on the control of sugar cataract as related to diabetes. Retinal changes in diabetes is also an important area of investigation. In particular, inhibitors of the enzyme Aldose Reductase (AR) have been shown to be effective in retarding many of the adverse effects of diabetes on lens and retina. From animal studies, it is clear that AR inhibitors will be of great importance in controlling the manifestations of diabetes in the human. In this regard, Dr. Deborah Carper has begun an important project on the isolation and characterization of the AR gene such that structural data obtained from the nucleotide sequence can be used for attempts to selectively inhibit AR gene expression in target cells.

Dr. Samuel Zigler is studying cataractogenesis and the structural modifications of lens proteins in the aging process and after oxidative insult. In collaboration with a noted extramural scientist, Dr. Frederick Bettelheim, he has used sophisticated biophysical techniques to demonstrate specific interaction among the crystallins with respect to their supermolecular organization.

Dr. Paul Russell has continued his study of lens membranes and has recently developed a monoclonal antibody to gamma-crystallin of the human lens. Study of the protein in development, aging and cataract should yield valuable information on normal and pathological lens functioning. In a similar vein, Dr. Donita Garland is studying the role of protein kinases in lens metabolism and how they regulate lens function through phosphorylation of endogenous lens proteins. In particular, she has found that alpha-crystallin, and the 19K and 26K intrinsic membrane proteins are phosphorylated.

2. Section on Cell Biology: Dr. Paul O'Brien has used the visual protein rhodopsin as a model for studying posttranslational modifications of proteins and their influence on cell function. He has found that rhodopsin is heavily acylated with the fatty acid palmitate. Acylation can be demonstrated in vitro using radiolabeled fatty acid. Moreover, endogenous fatty acid can be found bound to the purified protein using GLC and mass spectrometry.

3. Section on Retinal Metabolism: Collaboration among members of this section have produced excellent scientific results this last year. Dr. Barbara Wiggert and Dr. T. Michael Redmond have extensively characterized a unique extracellular protein of the retina, the Inter-photoreceptor-Retinoid Binding Protein (IRBP). With Dr. I. Gery of our Clinical Branch, it has been found that the protein is highly antigenic and produces an experimental auto-immune uveitus (EAU) reaction in rats. The protein is also found in the pineal gland, demonstrating a new and important link between retina and pineal.

In a striking advance, Dr. John Nickerson has successfully cloned the IRBP gene. A cDNA of 3500 base pairs has been obtained, a portion of which matches the amino acid sequence of an authentic IRBP tryptic peptide obtained by Dr. Redmond. In parallel, Dr. Nickerson has established that the IRBP mRNA is extraordinarily long (8000 bases), indicating a possibly unique mode of gene expression in the photoreceptor cell.

Dr. Athanassios Kyritsis has established a human retinoblastoma cell line in attachment culture and has shown that the cells are multipotential blast cells that are capable of differentiating into several cell types found in the adult eye. The origins of human retinoblastoma have been questioned for many years. Dr. Kyritsis' work has gone far in solving this problem, indicating that specific local conditions (humoral agents, substrata, etc.) could induce cells of neuronal or of glial phenotype in the tumor.

4. Section on Immunology: Dr. Igal Gery has continued his exciting work on the etiology of immune-mediated ocular diseases. As mentioned above, he has now established that the IRBP protein is highly antigenic and capable of producing a uveitogenic response in test animals. The response is somewhat similar to that produced by the well-known S-antigen but it does differ in several significant respects. Most importantly, this work establishes a new model for studying the pathophysiology of human uveitis.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00003-13 LVR

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Cataracts

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

PI:	Peter F. Kador	Ph.D.	Research Chemist	LVR, NEI
Others:	Hirofumi Terubayashi	M.D.	Visiting Associate	LVR, NEI
	Chihiro Nishimura	M.D.	Visiting Associate	LVR, NEI
	Takashi Shiono	M.D.	Visiting Associate	LVR, NEI
	Janet Sredy	Ph.D.	Guest Worker	LVR, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Vision Research

SECTION

Section on Lens and Cataract

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
3.25	3.0	0.25

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

Investigations are being conducted on the events leading to the formation of several types of cataract. Diabetic or sugar cataract formation initiated by the enzyme aldose reductase is being studied; moreover, the relationship between aldose reductase and other ocular diabetic complications such as retinopathy, corneal epitheliopathy, and basement membrane thickening is being investigated. Methods of delaying the onset of these complications through the pharmacological control of aldose reductase are also being developed.

The potential role of the enzyme pyrroline-5-carboxylate reductase in cataractogenesis is also being investigated. This enzyme, which possibly regulates cellular redox potentials and increases ATP levels through stimulation of the pentose shunt, is involved in the metabolic conversion of ornithine and glutamine to proline.

Hereditary cataract formation is also being studied in a strain of mice developed in our laboratory. These animals known as Philly mice develop osmotic cataracts by an as yet unknown mechanism.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00015-20 LVR

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

The Cell Biology of the Vertebrate Retina

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

PI:	Paul J. O'Brien	Head	LVR, NEI
Others:	Robert St. Jules	Staff Fellow	LVR, NEI
	Mary G. Wetzel	Staff Fellow	LVR, NEI

COOPERATING UNITS (if any)

Laboratory of Cell Biology, National Institute of Mental Health (M. Zatz)
LSU Eye Center, Louisiana State University (N. Bazan)
Department of Anatomy, University of Toronto (M. Irons)

LAB BRANCH

Laboratory of Vision Research

SECTION

Section on Cell Biology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
2.3	2.3	0.0

CHECK APPROPRIATE BOX(ES)

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

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

Posttranslational acylation of rhodopsin has been observed in both bovine and rat retinas. Detergent solubilized bovine rod outer segments have been employed to study the kinetic parameters of the acyltransferase activity which exhibited a Km of 40 μM for palmitoyl coenzyme A. No direct, short-term effects of light were found. Analysis of purified bovine rhodopsin revealed the presence of up to two moles of fatty acid per mole of rhodopsin, the major species being palmitic acid.

Both in vivo and in vitro experiments with rat retinas revealed incorporation of palmitate into newly-synthesized opsin in rod inner segments as well as into mature rhodopsin in rod outer segments, suggesting the existence of a fatty acid replacement mechanism. Palmitic acid also labeled phospholipids in the outer segment, principally phosphatidyl choline, which remained highly labeled long after a complete outer segment renewal period, suggesting an extensive turnover and reutilization of phospholipid components.

One by-product of phospholipid turnover is cytidine monophosphate. Gradient purified rat and bovine rod outer segments contain an active phosphatase which cleaves this nucleotide with a high degree of specificity in a manganese-dependent manner. This activity has been localized by histochemical techniques to the tips of rat rod outer segments, suggesting a role for this activity in photoreceptor shedding.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00016-18 LVR

PERIOD COVERED
October 1, 1984 to September 30, 1985

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
The Biochemistry of Normal and Dystrophic Retinas

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

PI: Paul J. O'Brien Head LVR, NEI

COOPERATING UNITS *(if any)*
School of Veterinary Medicine, University of Pennsylvania (G. Aguirre)

LAB/BRANCH
Laboratory of Vision Research

SECTION
Section on Cell Biology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.2	0.2	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.)*

Labeled fucose, heretofore thought to be a cone-specific sugar, has been shown to be incorporated into rhodopsin following intravitreal injection in both beagles and miniature poodles, the latter either normal controls or animals affected with inherited progressive rod-cone degeneration. The radiolabel could be released hydrolytically and was identified chromatographically as fucose.

Similarly, labeled palmitic acid was incorporated into rhodopsin following intravitreal injection in beagles as well as both normal and affected poodles. After hydrolytic release, the label was identified as palmitic acid by thin layer chromatography.

The posttranslational modification of rhodopsin by the addition of fucose and palmitic acid thus occurs in at least two strains of dogs but does not appear to be altered in the poodles affected with inherited retinal degeneration. However, labeling of phospholipids with palmitic acid in the affected poodles is half as great as in controls. This could be related to the reduced rate of outer segment renewal in the affected animals.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00023-07 LVR

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Macrophage and Lymphocyte Participation in Inflammatory Processes

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

PI:	Igal Gery	Ph.D.	Head, Section on Experimental Immunology	LVR, NEI
Others:	Cathy McAllister	Ph.D.	Extramural Fellow	LVR, NEI
	Barbara Vistica	B.A.	Microbiologist	LVR, NEI

COOPERATING UNITS *(if any)*

Laboratory of Developmental and Molecular Immunity, National Institute of Child Health and Human Development (R. Sekura)

LAB/BRANCH

Laboratory of Vision Research

SECTION

Section on Experimental Immunology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20205

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.)*

The project was extended this year to analyze the mode of action of pertussis toxin (Ptx). This component of the Bordetella pertussis bacteria was shown in another study (Project # Z01 EY 00069-08 LVR) to exhibit an outstanding adjuvant capacity, manifested by the enhancement of induction of experimental autoimmune uveoretinitis (EAU) in rats. In order to learn about the immunostimulatory activity of Ptx, its effects on lymphocytes and macrophages in vitro were determined; these cells are responsible for EAU development. The main findings: (1) Ptx stimulates proliferation of lymphocytes from human donors or various experimental animals. (2) Lymphocytes stimulated with Ptx also increase the production of various mediators ("lymphokines"), including interleukins (IL)-2 and -3. (3) Ptx stimulates the production and release of IL-1 by human monocytes or mouse peritoneal macrophages. The stimulatory effects of Ptx on lymphocytes and macrophages in culture may be related to its adjuvant activity. However,the optimal concentrations of Ptx for the effects in vitro were considerably higher than those producing the effect in vivo.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00069-08 LVR

PERIOD COVERED
October 1, 1984 to September 30, 1985

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

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

PI:	Igal Gery	Ph.D.	Head, Section on Experimental Immunology	LVR, NEI
Others:	Toichiro Kuwabara	M.D.	Head, Laboratory of Ophthalmic Pathology	LOP, NEI
	Cathy McAllister	Ph.D.	Extramural Fellow	LVR, NEI
	Shigeto Hirose	M.D.	Visiting Fellow	LVR, NEI
	Barbara Vistica	B.A.	Microbiologist	LVR, NEI
	David Chatham		Student	LVR, NEI

COOPERATING UNITS *(if any)*
Laboratory of Developmental and Molecular Immunity, National Institute of Child Health and Human Development (R. Sekura)

LAB/BRANCH
Laboratory of Vision Research

SECTION
Section on Experimental Immunology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
2.3	1.4	0.9

CHECK APPROPRIATE BOX(ES)

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

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

This project is aimed at learning about the pathogenesis of immune-mediated eye diseases. The main effort has been focused on investigating an animal disease, experimental autoimmune uveitis (EAU), which is considered a model for certain eye diseases in man. The main findings of the present studies include: (1) A retinal component, interphotoreceptor retinoid binding protein (IRBP), was found to be highly uveitogenic in experimental animals. Indeed, IRBP was found to be at least as efficient in inducing EAU in rats or monkeys as the well known S-antigen (S-Ag). The experimental disease induced by IRBP resembles grossly that induced by S-Ag, both in the eye and the pineal gland. The two diseases differ, however, in the pattern of responsiveness among rats with different genetic makeups. Rats of the BN and related strains are "low responders" to EAU induced by S-Ag, but are "high responders" when tested for EAU induced by IRBP. The finding that the retina contains a second major uveitogenic molecule, in addition to S-Ag, is of importance since (a) IRBP may participate in the etiology of certain uveitic conditions in man and (b) the animal disease it induces provides useful new data on immunopathogenic mechanisms in the eye. (2) Induction of EAU by S-Ag or IRBP is highly facilitated by an additional adjuvant, the B. pertussis bacteria (see also our Reports for FY 1982, 1983). The effect of the whole bacteria was found to be produced by a purified component, designated pertussis toxin (Ptx). Treatment of rats with Ptx reduced the threshold amount of S-Ag needed for induction of EAU, shortened the onset time and produced more severe pathologic changes. The mode of action of Ptx was further analyzed. Adoptive transfer of EAU was enhanced by Ptx treatment of the donor rats, but not by treatment of the recipient. These results suggest that Ptx enhances EAU development mainly by affecting the process of lymphocyte sensitization toward the uveitogenic antigen.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00070-08 LVR

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Vitamin A and Ocular Tissues

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

PI:	Barbara Wiggert	Ph.D.	Research Chemist	LVR, NEI
Others:	Ling Lee	M.S.	Chemist	LVR, NEI
	Michael Redmond	Ph.D.	Fogarty Fellow	LVR, NEI
	Gerald J. Chader	Ph.D.	Chief	LVR, NEI

COOPERATING UNITS *(if any)*

LSU Eye Center, New Orleans, LA (N. Bazan, T. Reddy)

LAB/BRANCH

Laboratory of Vision Research

SECTION

Section on Retinal Metabolism

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
3.3	2.3	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.)*

Interphotoreceptor retinoid-Binding protein (IRBP) was shown by enzyme-linked immunosorbent assay (ELISA) to be absent from monkey liver, testes, lens and cornea. IRBP was present in cerebral cortex, pineal, vitreous and aqueous humor. These results were confirmed by Western Blot. IRBP was localized to rod photoreceptor cells in monkey retina by means of immunoelectronmicroscopy. Rats immunized with purified IRBP developed intraocular inflammatory changes and pineal gland inflammatory changes. Incubation of Y-79 retinoblastoma cells grown in monolayer tissue culture with radiolabeled precursors showed IRBP to be synthesized and secreted by these cells. IRBP synthesis was markedly increased by butyrate treatment. Purified monkey IRBP was found to contain 6.64 mol. of endogenous fatty acids per mol. protein. 60% of the total fatty acid was physically attached; the remaining 40% was covalently bound. Monkey, human and bovine IRBP were compared by analytical peptide mapping which showed monkey and human IRBP to be very similar and distinct from bovine IRBP. Tryptic peptides from bovine IRBP were isolated by reversed-phased high performance liquid chromatography (HPLC) and sequenced. One such peptide was used to confirm the identity of an IRBP clone.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00105-06 LVR

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Structure and Composition of Lens Crystallins with Respect to Cataractogenesis

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

P.I.	J. Samuel Zigler, Jr.	Ph.D.	Research Biologist	LVR, NEI
Others:	Frederick A. Bettelheim	Ph.D.	Visiting Scientist	LVR, NEI
	Valerie A. Lucas	Ph.D.	Fogarty Fellow	
	Igal Gery	Ph.D.	Head, Section on Experimental Immunology	LVR, NEI

COOPERATING UNITS *(if any)*

Jules Stein Eye Institute, UCLA Medical School (J. Horwitz)
Institute of Biological Sciences, Oakland University, Rochester, MI (V. Reddy)

LAB/BRANCH

Laboratory of Vision Research

SECTION

Section on Lens and Cataract

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
2.2	2.2	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.)*

Numerous studies have demonstrated marked changes in the low molecular weight crystallins in human cataracts. We have identified three populations of these proteins, differing in molecular weight, but clearly related to each other immunochemically. The largest of the three species (MW = 24,000) is the component which rapidly disappears from the soluble protein fraction in cataractous tissue. We have identified this fraction, which is clearly related to γ-crystallin, as the material which previously has been called B_S-crystallin. It appears that this protein may play a key role in the process of opacification.

Oxidation accounts for many of the structural modifications seen in lens proteins during aging and cataractogenesis. We have been studying the effects of various oxidants on rat lenses in organ culture. Singlet oxygen and H_2O_2 are strongly toxic to lenses when present in the medium while the direct effects of the superoxide and hydroxyl radicals are minimal. We are now extending these studies to monkey lenses which are more similar to the human lens. A major advantage is the presence in these lenses of the yellow pigment found in human lenses which we have shown previously to be an effective photodynamic sensitizer.

Dr. Fred Bettelheim has initiated studies aimed at elucidating the nature of the supermolecular organization of the lens crystallins. By probing homo- and hetero-aggregates of the various crystallins for the presence of hydrophobic sites, charged sites, etc. one can deduce the types of interaction responsible for aggregation of the various crystallin mixtures. Results to date from ammonia sorption experiments indicate that specific types of interactions occur among the various crystallins and that the nature of the interactions varies depending upon the protein composition of the mixture.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00124-05 LVR

PERIOD COVERED
October 1, 1984 to September 30, 1985

TITLE OF PROJECT *(80 characters or less Title must fit on one line between the borders)*
Metabolism of the Retina and Pigment Epithelium

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

PI:	Gerald J. Chader	Ph.D.	Chief	LVR, NEI
Others:	Shay-Whey M. Koh	Ph.D.	Staff Fellow	LVR, NEI
	Athanassios P. Kyritsis	M.D.	Visiting Fellow	LVR, NEI
	Paul Madtes	Ph.D.	Staff Fellow	LVR, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Vision Research

SECTION
Section on Retinal Metabolism

INSTITUTE AND LOCATION
National Eye Institute, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
3.2	3.2	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)*

Characteristics of differentiation and development of neurons and glial cells of the neural retina and the retinal pigment epithelium are studied in cultured cells and in freshly dissected tissues. The primary model used is a human retinoblastoma cell line (Y-79) maintained in our laboratory.

1. These primitive neuroblasts can be induced to differentiate into cells of neuronal or glial characteristics.
2. Insulin receptors have been characterized on these cells.
3. A distinct β-adrenergic receptor is also present that is linked to adenylate cyclase.
4. Also the differentiating agent butyrate can induce high levels in Inter-photoreceptor Retinoid-Binding Protein making it probable that the retinoblastoma cells can take on photoreceptor-like characteristics.
5. Laminin treatment of the retinoblastoma cells allows for cell adhesion and also results in marked cell differentiation.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00135-13 LVR

PERIOD COVERED
October 1, 1984 to September 30, 1985

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Biochemistry of Retina and Pigmented Epithelium in Health and Disease

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

PI:	Helen H. Hess	M.D.	Medical Officer (Research)	LVR, NEI
Others:	J. Samuel Zigler, Jr.	Ph.D.	Research Biologist, Section on Lens and Cataract	LVR, NEI
	Toichiro Kuwabara	M.D.	Chief, Laboratory of Ophthalmic Pathology	LOP, NEI
	Irving Westney	B.S.	Biological Aid	LVR, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Vision Research

SECTION
Office of the Chief

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, MD 20205

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.)*

Investigations are being conducted on the biochemistry of the sensory retina, pigmented epithelium, choroid, vitreous and lens in normal and disease states, particularly in animal models of human retinal degenerations and in human retinal diseases. Effects of nutrition, genetic background, and environmental lighting (or darkness) on incidence and progress of retinal degeneration and associated posterior subcapsular cataracts (PSC) are being studied in pink-eyed and black-eyed strains of Royal College of Surgeons rats. An objective is to discover the mechanisms of ocular disease in RCS rats and explore possibilities for prevention or therapy. By 9 mo. of age, a fourth of pink-eyed but not black-eyed rats have mature cataracts. Factors involved in initiation and maturation of the cataracts are being examined. Dark-rearing of pink-eyed rats has shown that light initiates the PSC, and increased light exposure at early ages has demonstrated light to be a powerful factor in maturation of the cataract. Light also increases the rate of retinal degeneration. An hypothesis of the mechanism of damage to retina and lens is that a product of rhodopsin bleaching (perhaps free retinaldehyde) may act as a sensitizer to generate singlet oxygen ($^1O_2$), which can oxidize vitamin E and polyunsaturated fatty acids (PUFA) of phospholipids of degenerating rod photoreceptors. PUFA are broken down to water soluble toxic aldehydes, which can further damage the retina and also traverse the vitreous and affect the lens. Such aldehydes are detected in RCS vitreous shortly before the PSC appear. Diets that prevent maturation of the cataracts in pink-eyed rats reared in subdued lighting (1-3 footcandles inside the cage) are: (1) a purified diet of the American Institute of Nutrition (AIN-76); (2) a commercial rodent diet plus 25% sunflower kernels; and (3) a vegetarian rodent diet. Significant prevention of initial PSC has been achieved with (a) AIN-76 diet fortified with antioxidant factors; and (b) dark rearing.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00136-13 LVR

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Chemistry and Metabolism of the Lens

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

PI:	P. Russell	Ph.D.	Research Chemist	LVR, NEI
Other:	S. Sato	M.D.	Guest Worker	LVR, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Vision Research

SECTION

Section on Lens and Cataract

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.0	1.0	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.)*

Studies on the human lens have suggested that there is a differential regulation of the proteins in development. Work with a number of monoclonal antibodies indicates that maturation of human lens in terms of crystallin synthesis occurs at about the same time as the maturation of the retina. One of the low molecular weight proteins that begins to increase in content in the lens at about this time in development and become the major low molecular weight protein in the adult lens is absent in the cataractous zones of the lens. Immunological studies and high pressure liquid chromatography data have confirmed this decrease in microdissected lenses.

The proteins of the primate lens have also been investigated using the Rhesus monkey lens. In addition to characterization of the proteins and mRNA in the lens, the glycoproteins have been studied using lectin binding. Glycoproteins with apparent molecular weights of 120,000, 90,000, 67,000 and 64,000 are closely associated with and may be intrinsic to the membrane of the lens. Similar glycoproteins have been seen in the human lens also.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00146-04 LVR

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Migration in Proliferative Vitreoretinopathy

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

PI: Leonard M. Hjelmeland Ph.D. Expert LVR, NEI

COOPERATING UNITS *(if any)*

Reproductive Research Branch, NICHD (A. Chrambach); Surgical Neurology Branch, NINCDS (J. Bressler); Laboratory of Developmental Biology and Anomolies, NIDR (G. Grotendorst)

LAB/BRANCH

Laboratory of Vision Research

SECTION

Section on Retinal Metabolism

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
2.4	1.0	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.)*

Research is being conducted on the biological mechanisms which control chemotaxis and proliferation of neuroglia in proliferative vitreoretinopathy. Using wound repair as a general model, we have demonstrated that glial cells exhibit chemotaxis to platelet-derived growth factor (PDGF) in a fashion similar to that described in previous reports on smooth muscle and fibroblasts. In addition, we are characterizing and purifying a potent chemoattractant present in retina which attracts glial cells and possibly endothelial cells.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00148-12 LVR

PERIOD COVERED
October 1, 1984 to September 30, 1985

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

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

PI:	Gerald J. Chader	Ph.D.	Chief	LVR, NEI
Others:	Susan Gentleman	Ph.D.	Expert	LVR, NEI
	R. Theodore Fletcher	M.S.	Chemist	LVR, NEI
	Robert L. Somers	B.S.	Chemist	LVR, NEI
	C. Lal Kapoor	Ph.D.	Guest Worker	LVR, NEI

COOPERATING UNITS *(if any)*
Section on Ophthalmology, School of Veterinary Medicine, University of Pennsylvania (G. Aguirre); Department of Anatomy, Erasmus University, Rotterdam, The Netherlands (S. Sanyal)

LAB/BRANCH
Laboratory of Vision Research

SECTION
Section on Retinal Metabolism

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
3.3	2.3	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 roles of cyclic nucleotides and protein kinase in normal vision and in retinal degeneration have been further examined:

1. A direct gene-dose relationship has been found between the rds (retinal degeneration slow) gene and cyclic GMP phosphodiesterase activity in mutant mice.
2. Cyclic AMP-dependent protein kinase has been characterized in fetal and adult retina and in cultured human retinoblastoma cells.
3. Vanadate has been found to stimulate phosphotyrosine phosphorylation in quiescent Nakano lens cells but to not directly stimulate DNA synthesis by itself.
4. An in vivo system for studying calcium phospholipid-dependent protein kinase (C-kinase) has been established using the rat as a model.
5. A specific cyclic GMP phosphodiesterase of the retinal interphotoreceptor matrix has been found that is distinctly different from the light-activated, enzyme found in the retinal photoreceptor.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 000189-02 LVR

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Protein Kinases in Lens Function & Oxidation of Proteins in Cataractogenesis

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

PI: Donita L. Garland Ph.D. Expert LVR, NEI

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Vision Research

SECTION

Lens and Cataract Section

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20205

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.)*

The role of protein kinases in regulating metabolism in lens is being addressed by studying: 1) the protein kinases, and 2) the endogenous proteins that serve as substrates for the lens protein kinases. The focus of this study is on the purification of the protein kinases and the characterization of the phosphorylation of four endogenous substrates by cAMP-dependent protein kinases. The phosphorylated proteins are αcrystallin and 26K and 19K intrinsic membrane proteins. Comparison of the amino acid compositions of the 26K and 19K proteins suggest they are closely related. Detailed structural studies are in progress to determine how similar they are. Compounds that are thought to regulate the function of the 26K protein in vivo modulate the phosphorylation of the protein in vitro. Oxidative changes of lens proteins are thought to occur with aging and to contribute to the development of cataracts. The goals of this project are to determine: 1) the extent of oxidative modification of crystallins and metabolic enzymes in both normal and cataractous lenses; 2) the nature of the modifications and the mechanisms leading to the changes; and 3) the effect of the modifications on proteolysis of these proteins. Bovine and human lenses have been used for these studies. The carbonyl content of lens protein has been used as an indication of the extent of the oxidative modification. The carbonyl content is determined by reactivity with 2,4-DNPH. These studies have demonstrated in normal lenses there is a low but significant increase in carbonyl content as a function of age up to 100 years. Some types of cataracts and brunescent lenses have significantly increased carbonyl content. Noncataractous lenses obtained from diabetic individuals have levels varying from normal to significantly elevated carbonyl levels. In vitro mixed-function oxidase systems are being used to study the oxidative modification of metabolic enzymes and crystallin, and effects on proteolytic degradation. Experiments are in progress to identify the hydrazones.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 000190-02 LVR

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Characterization of Pathogenic and Antigenic Epitopes of Retinal S-antigen

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

PI:	Paul Stein	Ph.D.	Expert	LVR, NEI
Others:	J. Samuel Zigler, Jr.	Ph.D.	Research Biologist	LVR, NEI
	T. Kuwabara	M.D.	Head, Laboratory of Ophthalmic Pathology	LVR, NEI
	I. Gery	Ph.D.	Head, Section on Experimental Immunology	LVR, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Vision Research

SECTION

Section on Experimental Immunology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.1	1.1	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)*

S-antigen (S-Ag) induced experimental autoimmune uveoretinitis (EAU) is a recognized model for investigating the immunopathological mechanisms possibly involved in certain human uveitic diseases. The purpose of this project was to identify and isolate pathogenic and antigenic epitopes present on this unique autoantigen. Cyanogen bromide cleavage and S. aureus V8 digestion were utilized to produce fragments of the S-Ag. These were then characterized and isolated by electrophoretic and immunoblotting methods. Identification of antigenic epitopes was made possible using recently developed monoclonal antibodies specific for determinants present on the S-Ag molecule. Many of the fragments were also shown to contain antigenic determinants reactive to both monoclonal and polyclonal antibody probes. Pathogenic epitopes present of the isolated peptides were tested using the rat EAU model. Fragments of approximate molecular sizes of 45 kD, 25kD and 14 kD were found to be uveitogenic in microgram amounts.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00196-02 LVR

PERIOD COVERED
October 1, 1984 to September 30, 1985

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Molecular Genetics of the Eye and Ocular Diseases

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

PI:	John M. Nickerson	Ph.D.	Senior Staff Fellow	LVR, NEI
Others:	David Barrett	M.D.	Staff Fellow	LVR, NEI
	Diane Borst	Ph.D.	Guest Worker	LVR, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Vision Research

SECTION
Section on Retinal Metabolism

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
2.0	2.0	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.)*

Aspects of the molecular genetics of the eye and ocular diseases are being studied via recombinant DNA techniques. Clones and sequences from Interphotoreceptor-Retinoid Binding Protein (IRBP), its genes and mRNAs have been obtained. An expression retina cDNA library was screened successfully using antibodies against bovine IRBP. One clone (λIRBP-1) was obtained. This clone was used to screen another cDNA library from which 3500 bp (base pairs) of cDNA were obtained from two clones (λIRBP-2 and λIRBP-3). The clones unequivocally encode IRBP. There is an identity between the amino acid sequence of an authentic IRBP tryptic peptide and the deduced amino acid sequence from the nucleotide sequence of the cDNAs. We have found that a remarkably long mRNA (8000 bases) encodes IRBP. This is one of the longest mRNAs characterized to date and it apparently contains an extremely long untranslated region (4000 bases) within this mRNA. This may indicate a unique mode of IRBP gene expression in the photoreceptor cell. We have cloned approximately 22,000 bp of the IRBP gene locus to further investigate this gene and its regulation. Chromosome mapping of the IRBP locus may establish linkage with ocular diseases, for which we have begun collecting blood samples. A similar project with the δ-crystallin genes has been completed. The entire locus of 25,000 bp has been sequenced completely and analyzed.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00200-01 LVR

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Class II Antigen Expression in Ocular Disorders

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

PI:	Barbara Detrick-Hooks	Ph.D.	Expert	LVR, NEI
Others:	John J. Hooks	Ph.D.	Research Microbiologist	CB, NEI
	Chi-Choa Chan	M.D.	Staff Ophthalmologist	CB, NEI
	Merlyn Rodrigues	M.D.	Chief, Section of OP	LOP, NEI
	Robert Nussenblatt	M.D.	Chief, Section of COI	CB, NEI
	Caroline Percopo	B.A.	Biologist	CB, NEI

COOPERATING UNITS *(if any)*

Mark O.M. Tso, M.D., U. Of Illinois, Chicago, Illinois

LAB/BRANCH

Laboratory of Vision Research

SECTION

Section on Experimental Immunology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.7	1.45	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.)*

During the past year we have evaluated the possible role of class II antigens in ocular disorders. Class II antigens, HLA-DR in man and Ia in the mouse, are membrane bound glycoproteins encoded by genes of the MHC. These cell surface proteins play a pivotal role in immune responses, are present only on selected cell types, and their expression is regulated by the lymphokine, interferon-gamma. We have identified alterations in this system in both retinal degenerative disorders and in ocular inflammatory diseases (Uveitis, Sympathetic Ophthalmia and Sjogren's Syndrome). In the retinal degenerative disorder, retinitis pigmentosa, there is an alteration in the expression and regulation of class II antigens on blood monocytes. These findings were extended to demonstrate the presence of HLA-DR on a regulatory cell within the eye, the retinal pigment epithelial cell (RPE). The concept of activation of class II antigen on RPE cells is substantiated by both immunofluorescent and immunoperoxidase techniques which revealed the absence of HLA-DR on RPE cells from normal individuals and the presence of these antigens on RPE cells from patients with RP and inflammatory eye diseases. Moreover, the sequential development of class II antigens in experimental autoimmune uveitis (EAU) in the rat revealed the expression of class II antigens on RPE cells prior to and during the development of the disease. In another autoimmune disorder, Sjogren's Syndrome, we have identified the activation of class II antigens on salivary gland duct cells and are presently evaluating ocular tissue from these patients. These findings suggest that perturbation of ocular tissue via ocular inflammation or degeneration can lead to the modification of antigen expression on ocular cells. Furthermore the presence of HLA-DR on RPE cells may alter the pathogenicity of these ocular diseases.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00201-01 LVR

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Aldose Reductase Gene; Isolation, Characterization, Expression

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

PI:	Deborah Carper	Ph.D.	Biologist	LVR, NEI
Others:	Toshimichi Shinohara	Ph.D.	Biologist	LMDB, NEI
	Cheryl Craft	Ph.D.	Post-Doctoral Fellow	LDN, NICHD
	Jin Kinoshita	Ph.D.	Biochemist	LVR, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Vision Research

SECTION

Section on Lens and Cataract

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20209

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.0		

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

Aldose reductase (also known as alditol: $NADP^+$ 1-oxidoreductase) reduces aldose sugars to polyols and has been implicated as a primary factor in diabetic complications such as cataracts, retinopathy and neuropathy. cDNA clones for aldose reductase have been isolated and are now being characterized. A bovine retina λgt11 expression vector library was screened using antisera against rat lens aldose reductase. Several presumtive aldose reductase cDNA clones, approximately 300 base pairs in size, have been identified. Southern blot analysis determined that these cDNA clones are not homologous. One cDNA insert was cleaved by EcoRI restriction enzyme and purified by gel electrophoresis and subcloned into an M13 sequencing vector for DNA sequence determination. The DNA sequence for this cDNA insert revealed that there are no homologous sequences to known DNA sequences listed in the Genetic Sequence Data Bank. Using this sequenced cDNA and the other non-homologous 300 base pair cDNA clones, we plan to isolate and sequence larger cDNA fragments to obtain the entire coding region. Northern blot analysis indicates that the messenger RNA for aldose reductase is about 2 kilobases in size, suggesting a large untranslated region since the protein has a molecular weight of approximately 37,000.

One of our goals is to utilize the structural data obtained from the nucleotide sequence to selectively inhibit the aldose reductase gene in target cells. In addition, we plan to investigate the level of gene expression of aldose reductase in experimentally-induced diabetic and galactosemic animals.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00078-08 LOP

PERIOD COVERED
October 1, 1984, to September 30, 1985

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Histopathology of Human Dystrophies and Degeneration

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

PI:	Merlyn M. Rodrigues	M.D., Ph.D.	Chief, Section on Ophthalmic Pathology	LOP, NEI
Others:	Joseph Hackett	B.S.	Biologist	LOP, NEI
	Reginald Gaskins		Histologist	LOP, NEI

COOPERATING UNITS *(if any)*
Department of Ophthalmology, University of Iowa, Iowa City

LAB/BRANCH
Laboratory of Ophthalmic Pathology

SECTION
Section on Ophthalmic Pathology

INSTITUTE AND LOCATION
National Eye Institute, NEI, Bethesda, MD 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.2	0.1	0.1

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

Human corneal dystrophies and degenerations which have been clinically documented are studied as keratoplasty specimens with histochemical stains, scanning and transmission electron microscopy, and immunologic techniques in an attempt to elucidate pathogenetic mechanisms. This approach has provided insight into cell-to-cell relationships in the normal and diseased states. In patients with primary and and recurrent macular corneal dystrophy, intercellular and extracellular accumulation of fibrillogranular material was observed in the corneal stroma, Descemet's membrane, and corneal endothelium. The presence and production of collagen, glycoconjugates, and collagenase have been investigated with immunofluorescent electrophoretic, and chromatographic methods. The lectin binding patterns were compared in corneas from patients with macular dystrophy and control.

The characterization of amyloid in lattice corneal dystrophy and corneal amyloid degeneration was performed using immunohistochemical stains and biochemical analysis. Lack of AA reactivity was observed in corneal amyloid deposits. Keratoplasty specimens from granular corneal dystrophy and controls were examined by combinations of immunohistological stains, transmission electron microscopy, and SDS gel electrophoresis. In granular dystrophy, the deposits consisted of phospholipid with microfibrillar protein at the edges.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00096-07 LOP

PERIOD COVERED
October 1, 1984, to September 30, 1985

TITLE OF PROJECT *(80 characters or less Title must fit on one line between the borders)*
Clinicopathologic Studies of Human Ocular Diseases

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

PI:	Merlyn M. Rodrigues, M.D.,Ph.D.		Chief, Section on Ophthalmic Pathology	LOP, NEI
Others:	Joseph Hackett	B.S.	Biologist	LOP, NEI
	Reginald Gaskins		Histologist	LOP, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Ophthalmic Pathology

SECTION
Section on Ophthalmic Pathology

INSTITUTE AND LOCATION
National Eye Institute, NIH, Bethesda, MD 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)*

Patients with localized ocular diseases or with ocular manifestations of systemic disease are examined clinically, and photographic documentation is made of significant findings. Biopsy specimens or autopsy eyes from these patients are examined by electron microscopy and histochemical stains. Studies are performed on patients with ocular manifestations of systemic diseases.

Forty patients with acquired immunodeficiency syndrome (AIDS) were examined for ocular abnormalities. Twenty of these patients died and the eyes were obtained for culture and histologic examination. These patients have multiple opportunistic infections and neoplasms as the result of a severe depression of cellular immunity. Fifty percent of all patients with AIDS and 75% of the autopsy group have ocular signs attributable to AIDS. Ocular findings were confined to four major categories: cytomegalovirus retinitis (10 patients), retinal cotton wool spots (11 patients), conjunctival Kaposi's sarcoma (2 patients) and neuro-ophthalmic motility abnormalities (3 patients). Cytomegalovirus retinitis was a significant cause of visual loss. Seven of 40 autopsy eyes had hand-motion or worse vision prior to the patient' death because of CMV and progressed to involve the entire retina in three to six months resulting in a gliotic retina membrane. Disseminated systemic histoplasmosis was observed in a patient with AIDS.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00114-05 LOP

PERIOD COVERED
October 1, 1984, to September 30, 1985

TITLE OF PROJECT *(80 charecters or less Title must fit on one line between the borders)*
Histopathologic Studies of Animal Models of Human Ocular Diseases

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

PI:	Merlyn M. Rodrigues, M.D., Ph.D.		Chief, Section on Ophthalmic Pathology	LOP, NEI
Others:	Reginald Gaskins		Histologist	LOP, NEI
	Joseph Hackett	B.S.	Biologist	LOP, NEI
	Barbara Wiggert	Ph.D.	Research Chemist	LVR, NEI
	Gerald Chader	Ph.D.	Chief, Laboratory of Vision Research	LVR, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Ophthalmic Pathology

SECTION
Section on Ophthalmic Pathology

INSTITUTE AND LOCATION
National Eye Institute, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
0.2	0.1	0.1

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

Immunocytochemical staining of fresh frozen rhesus monkey retinas was performed using indirect immunofluorescence and immunoperoxidase (avidin-biotin-complex). Affinity-purified antibodies to interphotoreceptor retinoid-binding protein (IRBP) obtained from rabbits was used to localize IRBP on frozen sections. Fresh frozen pineal glands from the same species were stained by the avidin-biotin-peroxidase method. In addition, retinas from rod-dominant and cone-dominant species were examined. Immunocytochemical staining revealed localization of IRBP in the interphotoreceptor space of peripheral equatorial and posterior retina, with marked decrease in staining in the fovea. A transition zone was noted at the ora serrata, where staining was present in the peripheral retina up to the ora serrata, but was absent in ciliary epithelium. Cone-dominant retinas (chick and turtle) showed lack of reactivity to IRBP. Rod-dominant rat retina showed localization of IRBP to the interphotoreceptor space. Primate and rat pineal showed immunocytochemical localization of IRBP.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00145-03 LOP

PERIOD COVERED
October 1, 1984, to September 30, 1985

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Effects of Aging and Nutrition on the Retina and Retinal Pigment Epithelium

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

PI:	Martin L. Katz	Ph.D.	Staff Fellow	LOP, NEI
Others:	W. Gerald Robison, Jr.	Ph.D.	Chief, Section on Experimental Anatomy	LOP, NEI
	Masao Nagata	M.D.,Ph.D.	Visiting Associate	LOP, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Ophthalmic Pathology

SECTION
Section on Experimental Anatomy

INSTITUTE AND LOCATION
National Eye Institute, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
2.0	2.0	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.)*

Age-related changes in the retina and retinal pigment epithelium (RPE) have been characterized using morphological and biochemical techniques. One of the major age-related changes in the RPE is the progressive accumulation of lipofuscin, or age-pigment. We have continued experiments to elucidate factors which might play a role in RPE lipofuscin accumulation. Dietary deficiency in retinol was found to result in a reduced amount of lipofuscin deposition in the RPE. Excess dietary retinol also reduced the amount of RPE lipofuscin deposition in vitamin E-sufficient rats, but not in vitamin E-deficient rats. Phagocytosis by the RPE was also found to play a significant role in RPE lipofuscin accumulation. RCS rats with hereditary retinal degeneration were found to accumulate much less RPE lipofuscin than did congenic control animals whose retinas did not undergo degeneration. In addition to lipofuscin accumulation, a number of other age-related changes in the retina and RPE have been examined. Retinal capillary basement membranes in both the outer plexiform and ganglion cell layers were found to thicken during aging, retinal cell death accompanied senescence, and vitamin A metabolism in the retina-RPE complex was altered during aging.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00149-12 LOP

PERIOD COVERED
October 1, 1984, to September 30, 1985

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Ultrastructure and Function of the Cells and Tissues of the Eye

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

PI:	W. Gerald Robison, Jr.	Ph.D.	Chief, Section on Experimental Anatomy	LOP, NEI
Others:	Martin L. Katz	Ph.D.	Staff Fellow	LOP, NEI
	Masao Nagata	Ph.D.,M.D.	Visiting Associate	LOP, NEI
	Thomas C. Hohman	Ph.D.	Postdoctoral Fellow	LOP, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Ophthalmic Pathology

SECTION
Section on Experimental Anatomy

INSTITUTE AND LOCATION
National Eye Institute, NEI, Bethesda, MD 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
2.2	2.0	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.)*

Aldose reductase has been implicated in two histopathological hallmarks of diabetic retinopathy involving retinal capillary walls: 1) the selective loss in numbers of mural cells (intramural pericytes) from the capillaries; and 2) the thickening of the basement membranes which envelope the cells of the capillary walls. Mural cells contain aldose reductase, accumulate sorbitol, and appear to be more susceptible to incubation in high glucose than are endothelial cells. A thickening of capillary basement membrane ultrastructurally similar to that characteristic of diabetic retinopathy was induced in rat retinas by galactose feeding and was prevented by two structurally different inhibitors of aldose reductase. The diabetic-like thickening of retinal capillary basement membranes in galactose-fed rats was accompanied by other ultrastructural alterations mimicking changes typical of diabetic microangiopathy, such as multilamination, banding of collagen, and the formation of vacuoles and dense inclusions. Bovine, canine and human mural cells and endothelial cells from retinal capillaries are being grown in tissue culture so the role of aldose reductase and the alterations in basement membrane synthesis which relate to these cells in both normal and diabetic states can be studied under chemically defined conditions. Aldose reductase inhibitors provide a useful means for studies of,and perhaps even means for the prevention of diabetic retinopathy.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00193-02 LOP

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Molecular Biology of Hereditary Eye Diseases

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

PI:	George Inana	M.D., Ph.D.	Medical Officer	LOP, NEI
Others:	Seiichi Totsuka	M.D., Ph.D.	Visiting Fellow	LOP, NEI
	Carmelann Zintz	Ph.D.	Staff Fellow	LOP, NEI
	Thomas Dougherty	B.A.	Chemist	LOP, NEI

COOPERATING UNITS *(if any)*

Department of Ophthalmology, Juntendo University School of Medicine, Tokyo, Japan.
Department of Ophthalmology, Tohoku University School of Medicine, Sendai, Japan.
Tokushima University School of Medicine, Tokushima, Japan.

LAB/BRANCH

Laboratory of Ophthalmic Pathology

SECTION

Section on Experimental Pathology

INSTITUTE AND LOCATION

National Eye Institute, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
2.84	2.34	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.)*

Ornithine Aminotransferase Deficiency in Gyrate Atrophy: We have isolated a gene probe for the human ornithine aminotransferase (OAT), a mitochondrial enzyme which is deficient in gyrate atrophy patients. The gene probe is a λgt11 cDNA clone which was obtained from our retinoblastoma library through a Western screening method using the anti-human OAT antibodies. The complete DNA sequence of the cDNA was obtained. The OAT cDNA is 2073 basepairs (bp) long, and appears to be a nearly full length copy of the human OAT mRNA which is approximately 2.4 Kb in a Northern analysis. Numerous tryptic peptides were obtained from the pure OAT protein, and amino acid sequences of seven selected peptides were obtained by a microsequencing technique. A comparison of the amino acid sequences of the tryptic peptides to that derived from the OAT cDNA sequence revealed 111 out of 115 residues to be identical including a match of 20 consecutive amino acid residues. With our cDNA clone confirmed as a human OAT probe, we have begun to use it to examine the organization of the OAT gene in normal and gyrate atrophy patients. A gene clone for the human OAT has also been isolated and is being analyzed.

Hereditary Retinoblastoma: We are investigating the molecular basis of malignant transformation in hereditary retinoblastoma using cell culture and molecular genetic techniques. In view of the published data indicating that induction of hereditary retinoblastoma may involve a loss or inactivation of a gene on chromosone 13, we are investigating the possibility that the genomic DNA from normal human retina, when transfected on retinoblastoma cells, may be able to change the phenotype of retinoblastoma to that of a more 'normal' cell. To determine if retinoblastoma has a dominant or recessive malignant phenotype, retinoblastoma cells are being fused with normal cells, and the growth characteristics of the hybrid cells are being studied. Complementary DNA libraries made from the mRNAs of normal human retina and retinoblastoma are being screened for clones that represent differential expression in the two tissues, and such clones when isolated, will be identified and studied.

ANNUAL REPORT
NATIONAL EYE INSTITUTE
October 1, 1984 - September 30, 1985

REPORT OF THE CHIEF, LABORATORY OF SENSORIMOTOR RESEARCH

Robert H. Wurtz, Ph.D.

This is the seventh annual report of the Laboratory of Sensorimotor Research. The administrative event of the year was the consolidation of the laboratory into its permanent space on the tenth floor of the Clinical Center so that for the first time the laboratory is all under one roof. The scientific events centered on visual processing and oculomotor control, and the major work of each of the five permanent staff members of the laboratory is summarized below. Our goal is the understanding of the neural basis of these functions in man, but where analysis of neuronal activity in relation to behavior, or anatomical localization in relation to neuronal activity is required, old world monkeys are used in the research. These monkeys have visual and oculomotor performance that is very similar to that of man, and our knowledge of these systems in man is largely based on hypotheses derived from experiments on monkeys.

The role of the cerebral cortex in the initiation of pursuit eye movements has been investigated by Dr. Wurtz and his collaborators. An area of the cerebral cortex of the monkey, the middle temporal area, MT, has a large fraction of cells that respond selectively to the direction of stimulus motion. This concentration of similar types of neurons has led to the hypothesis that activity in this area is related to the perception of visual motion and the initiation of pursuit eye movements. Dr. Wurtz's group has been able to show previously that these cells have properties that would be required for the perception of apparent motion. They have also shown that damage to this area impairs the initiation of pursuit eye movements, those eye movements that keep the eye on a small moving target to allow further analysis of the target in spite of its motion. Experiments this year continued this analysis of the relation of MT to pursuit eye movements.

If a part of MT related to the peripheral visual field is damaged by the local injection of a neurotoxin (ibotenic acid), the monkey's ability to initiate a pursuit movement to the target is impaired. Once the target is acquired, however, pursuit is normal since the target is now on the fovea, not on the peripheral area. Following injection of a minute amount of ibotenic acid into the foveal area of MT, the monkeys showed two deficits, a retinotopic deficit and a directional deficit. The retinotopic deficit was similar to that seen following injections in the peripheral visual field: the monkey was unable to match its eye speed to the target speed when the target was moving in the contralateral visual field regardless of its direction. In addition, we observed a <u>directional deficit</u>: once the monkey had acquired the target, it was unable to match its speed with its pursuit movement when the target moved toward the side of the lesion. This deficit is identical to the classical neurological deficit in patients with large parietal cortex lesions, but since our deficit is the result of a tiny lesion, the localization can be made more precisely. Subsequent work has shown that this directional deficit is likely to result from invasion of

adjacent visual areas. The significance of this work is the demonstration for the first time that selective visual processing in an area of cerebral cortex is related to a behavior dependent on such processing. It is also significant for an understanding of pursuit eye movements since it shows the exact cerebral cortical area where the deficit shifts from a retinotopic visual base to a directional visual-motor base.

Work in Dr. David Robinson's group has focused on the contributions of brain areas to visual spatial attention. His previous studies have shown that neurons in the pulvinar of the thalamus have physiological properties consistent with a role in visual spatial attention. Subsequent experiments showed that changes in the activity of neurotransmitters in the pulvinar lead to changes in an animal's attentional behavior. The goal of experiments this year has been to assess the attentional contribution of cortical visual areas in humans.

Patients with suspected alterations in cortical function were studied in collaboration with Dr. Jon Currie of the Clinical Branch of the NEI. In the tests, all patients fixated a spot of light and reaction times were measured for responses to peripheral visual targets. When the location of these targets was predicted correctly by an antecedent visual cue (valid cue), then reaction times in normal subjects were faster than when the location was not predicted correctly (invalid cue). The hypotheses is that the cue draws attention to one location thereby facilitating responses at that location and slowing responses elsewhere. Individuals with damage to the parietal cortex were extremely slow in responding to targets in their affected visual field if their attention had just been shifted into their good visual field. Also, these patients were very slow in responding to any targets which were presented after illumination of the whole visual field (diffuse cue). This pattern of responses is unique to individuals with damage to the parietal lobes and suggests that such patients have a specific difficulty in shifting their attention once their intact visual field has captured their attention. Individuals with damage to the frontal lobes responded rapidly to all targets except those which stimulate the affected visual field and were preceded by diffuse cues. One of the affected brain regions suspected in schizophrenia is the frontal cortex and schizophrenics showed response patterns in this task which resembled those observed in patients with frontal lesions. Patients with Alzheimer's disease had a dramatic slowing of all of their responses such that the effects of the cue were lost. Humans with damage to their occipital lobes which caused hemianopsia showed no influence of the cue when it was presented in their "blind" visual field. These results suggest that the attentional system is dependent on visual data arising from the occipital cortex. Taken together, these studies show the exact attentional contribution of a particular part of the brain, and they provide hope that these types of tests can be an objective diagnostic tool for the evaluation of various disease states.

Dr. Goldberg's group has studied saccadic eye movements, those that move the eye rapidly from one part of the visual field to another. They had previously found that the frontal eye fields of the cerebral cortex contain three classes of neurons active before visually guided saccades: visual neurons that are visually responsive but do not discharge before purposive saccades made without a visual target; movement neurons that discharge equivalently before visually guided saccades and purposive saccades made without a visual target; visuomovement neurons that contain both visual and movement activity but discharge most actively before visually guided saccades. Experiments this year concentrated on the signal these cells convey to the brainstem for the initiation of saccades. Frontal eye field

neurons were antidromically activated by electrical stimulation of the superior colliculus, a brainstem oculomotor area. Two thirds of the neurons activated were either movement cells or visuomovement cells with predominantly movement activity. Only one visual cell was antidromically activated from the superior colliculus, although such cells make up 40% of the frontal cells which discharge in association with visually guided saccades. These results suggest that the frontal eye fields send a signal for the targeting and triggering of eye movements to the superior colliculus rather than a visual signal.

The anatomical definition of the frontal eye fields has not been clear because until the recent work in Dr. Goldberg's group there has not been a physiological description of the region. The area which now has been physiologically defined as the frontal eye fields is quite small, but occupies parts of two classical cytoarchitectonic regions, areas 8a and 45. A combined anatomical and physiological approach enabled a new and precise cytoarchitectonic definition of the frontal eye fields. The borders of the frontal eye fields were found by electrical stimulation and recording, and small electrolytic marking lesions placed at these borders. The area defined by the marking lesions had significantly larger pyramidal cells in Layer V, and one now can define a cytoarchitectonic region coterminous with the physiologically defined frontal eye fields by using layer V pyramidal cell size.

Work in Dr. Goldberg's group previously established that unilateral frontal eye field lesions result in a significant worsening of a monkey's ability to learn to make saccades to remembered targets, and the impaired motor performance of such saccades by monkeys who can make perfectly normal visually guided saccades. To see if the learning and performances were separable, monkeys were trained on remembered saccade tasks and then underwent unilateral surgical frontal eye field ablations. The monkeys had no difficulty retaining the ability to make remembered saccades. However, for several weeks after surgery all of their saccades into the the field contralateral to the lesion were slower and less accurate than saccades into the ipsilateral field. Saccades to briefly flashed targets were slower and less accurate than saccades to stable targets, and saccades to remembered targets were far slower and less accurate than those to briefly flashed targets. Thus although retention of previously learned behavior is not significantly affected by a frontal eye field ablation, the motor performance of that behavior is.

The stabilization of the visual scene following a saccade by an ocular following response has been studied by Dr. Miles' group. Previous work by his group has shown these responses are elicited by brief unexpected movements of the visual scene and that such responses are best when the movement began soon after the end of a saccade: the decline in responsiveness was exponential with a time constant of 60 msec. The magnitude of the post-saccadic enhancement was dependent on the amount of retinal stimulation during the antecedent saccade; when this stimulation was compromised—as when a vertical saccade was made on a grating pattern with vertically oriented stripes--subsequent enhancement of ocular following was much reduced. The post-saccadic enhancement of ocular following is largely due to the visual stimulation produced by the saccade sweeping the scene across the retina.

Work this year has concentrated on the stimulation conditions necessary to evoke the following movements. Contrary to expectation, en masse movement of the visual field was not the optimal stimulus for ocular following: responses could

be improved by partitioning the field into central and peripheral regions (center, 20-60° diameter) and reversing the image motion in the periphery so that center and surround now saw contrary movement. Since any tracking produced by motion in the periphery alone was always in the same direction as the stimulus, albeit weak, these anomalous effects of motion in the periphery must result from modulation of the system's sensitivity to motion at the center: in-phase suppression and antiphase enhancement. This peripheral modulation of ocular following probably assists in the tracking of 'objects'. Further, because this mechanism was only apparent when the central region was large--40° diameter was best--Miles suggested that, under normal conditions, the objects in question are generally nearby and stationary, their retinal images moving only because the observer moves; the contrary motion in the surround (due to the more distant background images) would then result from parallax. Using dichoptic presentation to allow each eye to be stimulated independently revealed that motion in the peripheral field of one eye could modulate the tracking induced by motion in the central field of the other eye (although limited to in-phase suppression): interocular transfer. This provides evidence that some part of the suppressive effect must occur at a site that receives inputs from both eyes and hence must be mediated by the CNS.

Other experiments with the field partitioned (center 20° diameter) showed that the conditioning and test stimuli had to be seen by the same region of retina in order to demonstrate enhancement. Indeed, when the two stimuli impinged on different regions, suppression was seen. The latter was particularly potent when the conditioning stimulus was seen by the peripheral retina and the test stimulus by the central retina: peripheral suppression. This suppression was brief, only affecting responses to test ramps initiated during--and up to 30 ms after--the conditioning stimulus. Peripheral suppression might function to prevent the ocular following system from tracking the visual disturbances caused by saccades: saccade-like movements confined to the center produced small transient ocular following responses whereas such movements of the periphery or of the whole field did not.

Dr. Optican has been working on both the adaptive control of eye movements and the representation of pictures by neurons in the visual system. The goal of the experiments in adaptive control has been to determine what strategies the brain may be using to compensate for the effects of disease and aging on eye movements. An adaptive control system exists that keeps the eyes from drifting immediately after a saccade, and this system depends on visual afference for its adjustments. Progress has been made this year in explicating the two components of this adaptation. One component is the adjustment of the tonic level of innervation needed to determine the final eye position, and the other is the control of the shape (size and time constant) of the transition from the phasic burst of innervation during the saccade to the final tonic level. Saccadic eye movements are so fast that they usually end before visual feedback can influence individual movements, but smooth pursuit movements are slow enough that visual feedback can be used to alter pursuit tracking. Hence it is not as necessary to keep the pursuit system calibrated with an adaptive controller. The time delays in the pursuit system, however, can cause eye movements to oscillate if the pursuit gain is too high. Thus the system is faced by two contradictory goals: the gain should be high to allow good tracking, but low to avoid oscillations. Under these circumstances, it would seem reasonable for an adaptive mechanism to try to keep the pursuit gain as high as possible without introducing oscillations. Indeed, Dr. Optican has shown that human subjects can increase the gain of their pursuit

system to compensate for peripheral muscle palsies. Such gain increases occur for movements both in the direction of action of the weakened muscle, and opposite to that direction. This is consistent with the fact that pursuit movements require the muscle in its agonist role to increase its force, while in its antagonist role it must decrease its force.

Dr. Optican has also collaborated with Dr. B. J. Richmond of NIMH in studying the pattern classification properties of neurons in striate and inferior temporal cortex of alert, behaving monkeys. Neurons were modeled as channels transmitting information about black and white pictures in their responses. By applying statistics and information theory they were able to prove that individual neurons are modulated by more than one stimulus feature, and that a neuron encodes this multivariate sensitivity by multiplexing different signals onto its output response. Thus, the response consists of modulation of both the number of spikes and their distribution. Furthermore, the amount of information transmitted in a response is uncorrelated with measures of response magnitude, e.g., spike count. Hence, neuronal responses cannot be interpreted simply by examining their magnitude. Instead, it is necessary to determine the spatial to temporal transformation code.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00045-07 LSR

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Visuomotor Properties of Neurons in the Thalamus

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

PI:	David Lee Robinson	Ph.D.	Research Physiologist	LSR, NEI
Others:	Steven E. Petersen	Ph.D.	Staff Fellow	LSR, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Sensorimotor Research

SECTION

Visuomotor Integration Section

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
3.6	2.0	1.6

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

We have been studying the effects of various brain lesions on the performance of a visual attention task. Normal subjects and patients fixated on a spot of light and responded to peripheral target lights. Reaction times in this task were fastest when the target was preceded by a cue at its location (valid cue); times were slower for cues at other locations (invalid cues). On some trials the whole visual field was weakly illuminated (diffuse cue).

Humans with lesions of parietal cortex performed well on most aspects of this task but were severely slowed when the cue drew their attention into their intact visual field and they had to respond to the target in their affected field. They also responded slowly to targets in both fields after diffuse cues. These data suggest that patients who have damage to their parietal cortex have a specific difficulty in shifting their attention once their intact visual field has captured their attention. No other patient population showed this effect. Humans with damage to the frontal lobes were only slowed when a diffuse cue was presented prior to a target in their affected visual field. People diagnosed as schizophrenics had slowed responses after diffuse cues prior to targets in their right visual field. Persons with occipital lesions which caused a hemianopsia showed no influence of the cue when it was presented in their "blind" visual field; this suggests that the attentional system is dependent on data arising from occipital cortex.

These studies are important in finding the specific contribution of brain areas to visual attention, and this approach may eventually be of diagnostic value for certain brain lesions.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00047-07 LSR

PERIOD COVERED

October 1, 1984, to September 30, 1985

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

Visual Processing in Brains following Cortical Ablation

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

PI:	Michael E. Goldberg	M.D.	Chief, NMS	LSR, NEI
Others:	Deng Shu-yi	M.D., Ph.D.	Visiting Fellow	LSR, NEI

COOPERATING UNITS *(if any)*

Laboratory of Neuropsychology, National Institute of Mental Health (L. Ungerleider, M. Mishkin);
Department of Neurology, Georgetown University School of Medicine (M. Goldberg)

LAB/BRANCH

Laboratory of Sensorimotor Research

SECTION

Neuro-Ophthalmologic Mechanisms Section

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.6	0.7	0.9

CHECK APPROPRIATE BOX(ES)

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

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

Monkeys were prepared with unilateral frontal eye field ablations. They were then trained on a series of oculomotor tasks. They could easily perform visually guided saccadic eye movements but were impaired in learning to make eye movements to remembered points.

To see if this deficit were primarily a learning deficit or a motor performance deficit, monkeys were trained on remembered saccade tasks and then underwent unilateral frontal ablations. These monkeys had no difficulty retaining the ability to make remembered saccades. However, for several weeks after surgery all of their saccades into the field contralateral to the lesion were slower and less accurate than saccades into the ipsilateral field. Saccades to briefly flashed targets were slower and less accurate than saccades to stable targets, and saccades to remembered targets were far slower and less accurate than those to briefly flashed targets. Thus ablation of the frontal eye fields causes both a learning and a motor performance deficit for saccades to briefly flashed or remembered targets.

Unilateral ablation of the superior colliculus caused short-lived deficits in saccade latency and motor performance, but no differential effect between saccades to visual targets and saccades to remembered targets.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00049-07 LSR

PERIOD COVERED

October 1, 1984, to September 30, 1985

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

Cerebral Cortical Mechanisms for Eye Movements and Visual Attention

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

PI:	Michael E. Goldberg	M.D.	Chief, NMS	LSR, NEI
Others:	Mark Segraves	Ph.D.	Staff Fellow	LSR, NEI
	Edmond J. FitzGibbon	M.D.	Senior Staff Fellow	LSR, NEI
	Deng Shu-yi	M.D., Ph.D.	Visiting Fellow	LSR, NEI

COOPERATING UNITS *(if any)*

Department of Anatomy, Howard University (G. B. Stanton)

LAB/BRANCH

Laboratory of Sensorimotor Research

SECTION

Neuro-Ophthalmologic Mechanisms Section

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
3.6	2.3	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 frontal eye fields of the cerebral cortex contain three different populations of neurons which are active before visually guided saccades: visual neurons responsive only to light, movement neurons active before purposive saccades, and visuomovement neurons which have both visual and movement activity. Since the frontal eye fields are known to project to the superior colliculus by anatomical methods, antidromic electrical stimulation from the superior colliculus was performed on behaviorally and physiologically characterized frontal neurons to see if any cell types projected preferentially. Of the antidromically activated neurons, two thirds were movement or visuomovement with very strong movement activities. Fewer than 2% were purely visual. One third of the neurons discharged during active fixation or were excited by the signal to make a saccade, but had no specific movement field.

The frontal eye fields occupy parts of two classically defined cytoarchitectonic areas, 8a and 45. Physiological identification of the borders of the frontal eye fields and quantitative measurement of cell size revealed a new cytoarchitectonic region whose hallmark is large neurons in Layer V. This region is coterminous with the physiologically identified frontal eye fields and bridges the border between areas 8a and 45.

Monkeys can be trained to adjust the gain of saccades within a few hundred trials. When a monkey has been trained to make an adapted saccade of a certain dimension, stimulation of the superior colliculus results in the generation of an unadapted rather than an adapted saccade.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00109-05 LSR

PERIOD COVERED

October 1, 1984, to September 30, 1985

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

Visual Motion Processing in the Primate Brain

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

PI:	Robert H. Wurtz	Ph.D.	Chief	LSR, NEI
Others:	Max R. Dursteler	M.D.	Visiting Scientist	LSR, NEI
	Hidehiko Komatsu	Ph.D.	Visiting Scientist	LSR, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Sensorimotor Research

SECTION

Visuomotor Integration Section

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
4.7	2.5	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.)*

In the primate cerebral cortex, visual information processing begins in the striate cortex and continues into extrastriate areas. The middle temporal area (MT) is one of these extrastriate visual areas, and it is distinguished by having a high proportion of cells that respond to stimuli moving within a restricted range of directions and velocities. Our work on this area in previous years has concentrated both on the relation of cells in this area to the perception of visual motion and to the initiation of pursuit eye movements in response to moving stimuli. This year we have investigated the relation of area MT to the maintenance of pursuit eye movements once a visual target is acquired and the target falls on the fovea. To do this, we trained monkeys to pursue a moving visual target and measured with the magnetic search coil technique their ability to do so. We then located the foveal area of MT with microelectrodes and injected into this and adjacent areas a neurotoxin, ibotenic acid, which kills cells but leaves fibers unaffected. We first observed a retinotopic deficit that we had seen previously following injections related to the more peripheral visual field: the monkey was unable to match his eye speed to the target speed when the target was moving in the contralateral visual field near the fovea, regardless of its direction. In addition, we observed a directional deficit: once the monkey had acquired the target, he was unable to match its speed with a pursuit movement when the target moved toward the side of the brain with the lesion. The deficit was present with stimulus motion in any part of the visual field. This deficit in the monkey following a tiny localized cortical lesion is similar to the classical neurologic deficit in man following damage to large cortical areas: a deficit in pursuit toward the damaged side of the brain.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00152-03 LSR

PERIOD COVERED

October 1, 1984, to September 30, 1985

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

Adaptive Changes in Eye Movements

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

PI: Lance M. Optican Ph.D. Research Biomedical Engineer LSR, NEI

COOPERATING UNITS *(if any)*

Department of Neurology, Johns Hopkins University Medical School (D. Zee)

LAB/BRANCH

Laboratory of Sensorimotor Research

SECTION

Oculomotor Control Section

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.5	0.9	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.)*

Clear vision requires that eye movements keep images stationary on the retina. When the eyes need to change fixation to look at novel objects, or when the eyes must follow smoothly moving objects, the saccadic and smooth pursuit eye movement systems come into play. Saccades have high velocities and abrupt endings. These characteristics allow the eyes to get on target quickly, minimizing the amount of time that vision is interrupted. The pursuit system smoothly matches eye velocity to target velocity, keeping images from slipping on the retina. Following central or peripheral diseases or injuries these eye movements may become affected by the weakness of one or more extraocular muscles. We have shown in monkeys that retinal image slip is sufficient to elicit adaptive changes in saccadic innervation. The required changes consist of two components: an adjustment of the tonic level of innervation needed to determine the final eye position, and control of the shape (size and time constant) of the transition from the phasic burst of innervation during the saccade to the final tonic level. Smooth pursuit movements depend on retinal feedback to alter eye velocity to match target velocity. So, it would seem that adaptive control of the smooth pursuit system would not be necessary. However, there is a 130 millisecond delay before visual events can influence pursuit eye movements, which creates two contradictory goals: the pursuit gain must be high for good tracking, but low to avoid oscillations. An adaptive controller could resolve this contradiction. We have shown that human subjects can alter the gain of their pursuit systems to compensate for peripheral muscle weakness. Such gain increases occur for movements both in the direction of action of the weakened muscle, and opposite to that direction. These results show that adaptive mechanisms are sensitive to retinal image slip. Work is continuing on the study of adaptive systems to determine how neuronal networks might be constructed to make use of error signals for the control of eye movement systems.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00153-03 LSR

PERIOD COVERED

October 1, 1984, to September 30, 1985

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

Adaptive Regulation in Primate Oculomotor System

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

PI:	Frederick A. Miles	D.Phil	Chief, OCS	LSR, NEI
Others:	Kenji Kawano	M.D., Ph.D.	Visiting Scientist	LSR, NEI
	Lance Optican	Ph.D.	Senior Staff Fellow	LSR, NEI
	Reuben Gellman	Ph.D.	Visiting Fellow	LSR, NEI
	James Carl	M.D.	Senior Staff Fellow	LSR, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Sensorimotor Research

SECTION

Oculomotor Control Section

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
4.6	2.7	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.)*

Experiments were concerned with the initial ocular following responses to transient ramp movements of the visual scene in monkeys. These tracking movements are important in the stabilization of gaze which is so necessary for good visual acuity. We had previously shown in monkeys that responses have short latency (50 msec) and are transiently enhanced after saccadic eye movements due to the associated visual disturbance. We now report that en masse movement of the visual scene is not the optimal stimulus for ocular following: Responses could be improved by partitioning the field into central and peripheral regions (center, 20-60° diameter) and, with gaze centered, reversing the image motion in the periphery so that center and surround now saw contrary movement. Since tracking produced by motion in the periphery alone was always in the same direction as the stimulus, we conclude that these anomalous effects of motion in the periphery result from modulation of the system's sensitivity to motion at the center: in-phase suppression and antiphase enhancement. We suggest that this peripheral modulation assists in the tracking of 'objects'. Further, because this modulation was only apparent when the central region was large--40° diameter was best--we suggest that, under normal conditions, the objects in question are generally nearby and stationary, their retinal images moving only because the observer moves; the contrary motion in the surround (due to the more distant background images) would then result from parallax. Using dichoptic presentation to allow each eye to be stimulated independently revealed that motion in the peripheral field of one eye could modulate the tracking induced by motion in the central field of the other eye: interocular transfer. This provides evidence that some part of the effect must occur at a site that receives inputs from both eyes and hence must be mediated by the CNS.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00199-01 LSR

PERIOD COVERED

October 1, 1984, to September 30, 1985

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

Smooth Pursuit Eye Movements in Humans

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

PI:	James R. Carl	M.D.	Senior Staff Fellow	LSR, NEI
Others:	Reuben Gellman	Ph.D.	Visiting Fellow	LSR, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Sensorimotor Research

SECTION

Neuro-Ophthalmologic Mechanisms Section

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20205

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
1.4	1.4	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 dynamics of smooth pursuit eye movements in normal human subjects were evaluated with the search coil method. The influence of the position and velocity of a target were investigated by using a computer-controlled spot of light to present these stimulus features separately and in various combinations. The combination of search coil recording and computer control of the experiments allowed us to obtain far higher resolution of the early part of the pursuit response than has previously been reported. The responses to all stimuli were surprisingly machine-like, with a latency of only 100 ± 4 (SD) ms. The accelerations of the initial part of the response were low ($40\text{-}50^{\circ}/s^2$) and nearly independent of stimulus velocity in the range $5\text{-}40^{\circ}/s$. Furthermore, a change in position alone, without an attendant change in velocity, produced comparable accelerations and latencies. Accelerations of the later parts of the response were much higher and depended strongly on stimulus velocity. When position and velocity information were in conflict, the response was briefly toward the position component and then reversed toward the velocity component.

These observations, along with data collected under an open-loop condition, lead us to surmise that there are several distinct phases--and probably mechanisms--present in the pursuit system. We are currently extending these experiments to stimuli that cover most of the field of vision, and also to stimuli that require adaptation of the system in order to accurately track the target. These findings have allowed us to model the pursuit system in humans in more detail and to make predictions about the tracking deficits that might be present with failures of the various sub-systems. We plan to evaluate these individual components in patients with pursuit deficits to identify the nature and possible location of their abnormality.

ANNUAL REPORT
NATIONAL EYE INSTITUTE
October 1, 1984 - September 30, 1985

REPORT OFTHE CHIEF, LABORATORY OF MOLECULAR AND DEVELOPMENTAL BIOLOGY

Joram Piatigorsky, Ph.D.

This fourth year of the Laboratory of Molecular and Developmental Biology has been a whirlwind of scientific advancement and organizational change. Dr. Gabriel Vogeli has left the NIH, reducing to three the number of independent research groups in the LMDB. Each of the remaining groups has expanded proportionately with consequent increase in productivity. The laboratory has been subdivided into three sections which will be effective in fiscal year 1986. These sections will be under the leadership of Dr. Peggy S. Zelenka (Section on Cell Differentiation), Dr. Toshimichi Shinohara (Section on Molecular Biology) and Dr. Joram Piatigorsky (Section on Molecular Genetics). As in the past, each group will continue to interact extensively through laboratory meetings and scientific exchanges.

Key advances have marked each research group in the LMDB this year. My group has effected a change in emphasis from gene structure to gene function. Crystallin gene promoters have been analyzed in vitro, in cultured cells and in transgenic mice. Peggy Zelenka's group has established the putative relationship between lens cell growth and phosphatidylinositol turnover in experiments using cultured cells. Moreover, this group has expanded its efforts to the molecular level by making the striking observation that the proto-oncogene, c-myc, is regulated during chicken lens cell growth and fiber differentiation. Finally, Toshimichi Shinohara's group has shifted its work to an analysis of the retinal S-antigen. In addition to its possible importance in uveitis, S-antigen has been highlighted recently by new evidence indicating that it has a role in regulating the visual cycle by interaction with rhodopsin. Thus, progress in the identification of crystallin gene regulatory sequences, lens cell regulatory biochemical pathways and visual cycle regulatory genes has opened new opportunities for a greater understanding of the visual system and for possible, future intervention at the molecular level, as appropriate, in the case of disease. A brief review of the major findings of each group follows below.

My group studying crystallin genes has progressed greatly in its ability to study expression, however, it has also made significant strides in continuing to elaborate crystallin gene structure. The entire δ-crystallin gene locus (25 kb) was sequenced, revealing 2 extremely similar genes, 3.9 kb apart, tandemly arranged and containing 17 exons apiece. Although no cDNA has been found yet for δ2, the absence of stop codons in the δ2 gene and the 91% sequence identity of the δ-crystallin proteins encoded in the two δ genes suggest that δ2 is a functional gene. This idea was supported by experiments demonstrating that the δ2 gene promoter is active in a Hela cell extract and in its ability to drive the bacterial chloramphenicol acetyltransferase gene (CAT) in cultured lens cells. However, we found interestingly that the δ1 gene promoter is more

active than the δ2 promoter in both of these assays. The puzzle thickened when we found that RNA derived from the δ1 cloned cDNA could produce both the 50K and 48K δ-crystallin polypeptides in a reticulocyte lysate. Possibly this is due to the use of two functional initiation sites for translation on the mRNA. Sequence analysis of a chicken β-crystallin cDNA (β19/26) raised the possibility that a similar situation exists for this mRNA as well. Thus, as the mysteries of crystallin synthesis are being resolved, fascinating regulatory controls operating at the transcriptional and translational level are becoming recognized.

Particularly exciting advances have been made in the area of crystallin gene expression. We have demonstrated that transcription of crystallin genes can be studied in a Hela cell extract. These in vitro experiments mapped functional boundaries of the core promoter of the δ1 gene and showed that Spl, the Hela cell transcription factor required for SV40 transcription, is also used by the δ1 promoter. In addition, experiments indicated that upstream sequences required for the in vivo function of the murine δA-crystallin promoter are not necessary for in vitro function in the Hela cell extract. Finally, a collaborative effort between the LMDB and Dr. Heiner Westphal's section (LMG, NICHD) has resulted in two lines of transgenic mice containing a murine αA-crystallin promoter (-364 to +45) fused to the bacterial CAT gene. The crystallin promoter directs the expression of the CAT gene specifically to the lens. This promoter functions at the correct time during development, namely at the beginning of lens development. These experiments clearly have important implications for both basic studies of gene expression and eventual practical applications.

The group headed by Dr. Peggy Zelenka has made significant progress in understanding the control of lens cell division and fiber cell differentiation. They have divided the phosphatidylinositol degradation rate into a rapid phase (associated with binding of calcium-mobilizing agonists) and a slower phase (associated with levels of DNA synthesis). Their experiments provide evidence that these two phases are controlled independently, and that the slower rate is associated with the regulation of cell division. In addition, this group advanced their analysis of an arachidonic acid metabolite found in cultured lens cells treated with various growth factors. This interesting metabolite appears to be a product of the cyclo-oxygenase pathway. It is synthesized by lens epithelial cells of different species (i.e., mouse and chicken) but not by non-lens cells which have been tested. Importantly, the metabolite stimulates DNA synthesis and is mitogenic when added to quiescent cultures of murine lens epithelial cells. Further exciting results have shown that the proto-oncogene, c-myc, is expressed in dividing lens epithelial cells but not in the non-dividing fiber cells, and that the amount of c-myc mRNA is transiently elevated in cultured lens epithelia which are stimulated to differentiate into fiber cells by lentropin. Finally, both insulin and insulin-like growth factor (IGF) receptors have been followed on the surface of lens cells during development. The results suggest that IGF receptors are associated with fiber cell differentiation and that insulin receptors are associated with lens cell division. Taken together, the recent experiments of this group are beginning to identify critical components in the biochemical pathways regulating lens cell growth and differentiation.

The group headed by Dr. Toshimichi Shinohara has started a new course of investigation, namely an analysis of S-antigen at the gene level. This important protein has generated renewed interest in view of the recent evidence suggesting that it regulates phophodiesterase activity in the rod outer segments by interacting with phosphorylated rhodopsin. S-Antigen cDNAs have been isolated from a bovine retina expression library and approximately two-thirds of the protein coding region has been sequenced. A partial amino acid sequence has also been obtained from the N-terminal region of purified S-antigen in order to be able to identify the translation initiation codon within the cDNA. Northern blot hybridization experiments have shown that S-antigen mRNA is approximately 1.7 kb in size and is present both in the bovine retina and the pineal gland, but not elsewhere. In situ hybridization experiments have localized both S-antigen and opsin mRNAs in the rod inner segments of the retina and in pinealocytes. Thus, this group is rapidly obtaining and characterizing probes to explore differential gene expression in the retina, and is providing a valuable database for furthering our knowledge of the mechanism of the visual cycle. In addition, production of altered forms of S-antigen from cDNAs should provide valuable information concerning the mechanism by which this protein induces uveitis in rats.

Members of the LMDB have conducted numerous collaborative projects with other laboratories in 1985. These include analysis of the murine γ-crystallin promoter (with Drs. M. Breitman and L-C. Tsui, University of Toronto, Toronto, Candad), production of transgenic mice (with Dr. H. Westphal, LMG, NICHD), development of lens cell lines which respond to cloned crystallin promoters (with Dr. J. Reddan, Eye Research Institute, Oakland University, Rochester, Michigan), chromosomal mapping of crystallin genes in mice (with Dr. R. Church, Emory University Medical School, Atlanta, Georgia) and humans (with Dr. F-T. Kao, Eleanor Roosevelt Institute for Cancer Research, Denver, Colorado), sequencing of the δ-crystallin gene locus (with Dr. J.M. Nickerson, LVR, NEI and Dr. D. Filpula, Genex Corp., Gaithersburg, Maryland), determination of the structure of an arachidonic acid metabolite (with Dr. A. Ferretti, USBA, Agricultural Research Center, Beltsville, Maryland), measurement of insulin and IGF receptors on lens cells (with Drs. F. dePablo and L. Bassas, NIADDK), analysis of S-antigen cDNAs (with Dr. D. Klein, LDN, NICHD), induction of uveitis by S-antigen (with Drs. P. Stein and I. Gery, LVR, NEI) and isolation of aldose reductase cDNA (with Dr. D. Carper, LVR, NEI).

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00126-04 LMDB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Crystallin Genes: Structure Organizations Expression and Evolution

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

PI:	Joram Piatigorsky	Ph.D.	Chief	LMDB, NEI
Others:	Teresa Borras	Ph.D.	Staff Fellow	LMDB, NEI
	Ana B. Chepelinsky	Ph.D.	Expert	LMDB, NEI
	Barbara Norman	B.S.	Chemist	LMDB, NEI
	James W. Hawkins	Ph.D.	Fogarty Fellow	LMDB, NEI
	Mark A. Thompson	Ph.D.	Staff Fellow	LMDB, NEI
	Eric F. Wawrousek	Ph.D.	Staff Fellow	LMDB, NEI

COOPERATING UNITS *(if any)*

See next page

LAB/BRANCH

Laboratory of Molecular and Developmental Biology

SECTION

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20894

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
11.5	9.5	2.0

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

Considerable progress has been made on the structure and expression of the crystallin genes of the lens. The entire 25 kb locus comprising the 2 δ-crystallin genes and the β35 and β19/26 cDNAs of the chicken have been sequenced. The δ-crystallin genes are remarkably similar, with each containing 17 exons and encoding proteins with 91% sequence identity. Surprisingly, however, the 48k and 50k δ-crystallin polypeptides could both be derived in experiments using a cloned δ1 cDNA. The promoter regions of the 2 δ genes are very similar and GC-rich, although a CAAT box is present only in the δ1 promoter. The chicken β35 was found to be homologous to the mammalian βB1; both have the characteristic N-terminal, alternating pro-ala sequence. The human and chicken αA-crystallin gene have been isolated; the chicken gene has been fully sequenced and the human gene partially sequenced. The murine αA-crystallin gene has been mapped to chromosome 17. Functional studies have shown that the δ1 gene promoter is more active than the δ2 promoter in a Hela cell extract and in its ability to drive the bacterial chloramphenicol acetyltransferase (CAT) gene in transfected cultured lens cells. Competition experiments indicate that the δ1 promoter utilizes Spl as a transcription factor in a Hela cell extract. The αA-crystallin promoter was shown to be extremely tissue-specific both in cultured cells and in transgenic mice. Analysis of the murine αA-crystallin promoter suggested the existence of several elements, including an upstream enhancer-like sequence required for *in vivo* expression.

Additional Personnel Engaged on Project:

George Thomas	Ph.D.	Staff Fellow	LMDB, NEI
Charlotte Peterson	Ph.D.	Guest Worker	LMDB, NEI
Gokul C. Das	Ph.D.	Visiting Scientist	LMDB, NEI
Cynthia Jaworski	M.S.	Chemist	LMDB, NEI
Bernd Sommer	B.S.	Guest Worker	LMDB, NEI
Diana Parker	B.S.	Guest Worker	LMDB, NEI

Cooperating Units:

Martin Breitman	Ph.D.	Hospital for Sick Children Toronto, Canada
Lap-Chee Tsui	Ph.D.	Hospital for Sick Children Toronto, Canada
John Reddan	Ph.D.	Oakland University Rochester, Michigan
Robert Church	Ph.D.	Emory University Medical School, Atlanta, Georgia
Heiner Westphal	M.D.	LMG, NICHD, NIH
John M. Nickerson	Ph.D.	LVR, NEI, NIH
David Filpula	Ph.D.	Genex Corp., Gaithersburg, Maryland

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00127-09 LMDB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Plasma Membrane Composition and Biosynthesis in Chick Lens Fibers and Epithelia

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

PI:	Peggy Zelenka	Ph.D.	Geneticist	LMDB, NEI
Others:	Luke Pallansch	Ph.D.	Staff Fellow	LMDB, NEI
	Malini Vatal	Ph.D.	Visiting Fellow	LMDB, NEI
	Pravendra Nath	Ph.D.	Visiting Fellow	LMDB, NEI

COOPERATING UNITS *(if any)*

Laboratory of Cell and Developmental Biology, NIADDR (F. de Pablo)
Diabetes Branch, NIADDR (L. Bassas)
Beltsville Agricultural Research Center, Beltsville, MD (A. Ferretti)

LAB/BRANCH

Laboratory of Molecular and Developmental Biology

SECTION

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20894

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
4.2	4.2	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 seeks to determine the role of plasma membrane lipids in the regulation of lens epithelial cell division and differentiation. Turnover of phosphatidylinositol and polyphosphoinositides has been shown to increase markedly within seconds after the addition of growth factors to quiescent lens epithelial cells. Thereafter, the rate of cell division is proportional to the rate of phosphoinositide degradation. A similar correlation between phosphatidylinositol degradation and cell division has been observed in embryonic chicken lens epithelia during development. Since phosphatidylinositol is rich in arachidonic acid, the arachidonic acid metabolites synthesized by cultured lens epithelial cells have been characterized in an effort to understand the physiological role of phosphatidylinositol degradation. A unusual metabolite of arachidonic acid has been isolated which is mitogenic for cultured lens cells. Specific alterations in phosphatidylinositol metabolism are being correlated with the levels of insulin receptors and IGF receptors present in embryonic chicken lens epithelia at different developmental stages.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z0 EY 00132-04 LMDB

PERIOD COVERED

October 1, 1984 to September 30, 1985

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

Sturcture and Function of S-Antigen and its Gene

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

PI:	Toshimichi Shinohara	Ph.D.	Biologist	LMDB, NEI
Others:	Graeme Wistow	Ph.D.	Fogarty Fellow	LMDB, NEI
	Albine Katial	Ph.D.	Staff Fellow	LMDB, NEI
	Cheryl Craft	Ph.D.	Post Doctoral Fel.	LDN, NICHD
	Theo VanVeen	Ph.D.	Guest Worker	LDN, NICHD
	John Parchue		Student	
	Deborah Carper	Ph.D.	Biologist	LVR, NEI
	Paul Stein	Ph.D.	Expert	LVR, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Molecular and Developmental Biology

SECTION

Molecular Biology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20894

TOTAL MAN-YEARS	PROFESSIONAL	OTHER
5	4.9	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)*

Complementary DNA (cDNA) and gene for bovine retinal S-antigen have been isolated and characterized. cDNA clones were isolated from a λgtll cDNA expression library using polyclonal S-antigen antiserum and were further verified using monoclonal antisera. The largest cDNA observed was 500 base pairs long. This was used subsequently to screen cDNA clones from a λgtl0 retinal library, yielding fragments up to 900 base pairs in length. Polypeptides synthesized by the 500 base pair cDNA clone was recognized by 2 different monoclonal antibodies. In contrast, polypeptides produced by cDNA clones smaller than 400 base pairs were recognized by only one monoclonal antibody. The 500 base pair S-antigen cDNA was found to hybridize specifically to mRNA (approximately 1700 $\pm$ 200 base pair) prepared from bovine retina and pineal gland but not to mRNA from liver, cerebral cortex and cerebellum. S-antigen was highly purified by HPLC and determined polypeptide sequence (19 AA) at near N-terminal. The DNA sequences of 500 and 900 base pair cDNA were determined using dideoxy method. 900 base pair cDNA covers the 240 amino acid residues from carboxyl terminal. The polypeptide deduced from DNA sequence is identical in sequence with known S-antigen peptides. The S-antigen polypeptide (240 AA residue) expressed in high yield expression bacterial system did not induce uveitis in the experimental animals.

S-antigen and opsin probes were used for in situ hybridization analysis. S-antigen and opsin mRNAs were detected only rod cell inner segments and pinealocytes but not cone cells.