ANNUAL REPORT
NATIONAL EYE INSTITUTE
October 1, 1987 - September 30, 1988

REPORT OF THE SCIENTIFIC DIRECTOR

Jin H. Kinoshita, Ph.D.

During this past year, we were very pleased that three of our NEI intramural scientists received well deserved recognition. The research accomplishments of these three scientists have brought great distinction to the NEI.

Dr. Robert Wurtz, Chief of the Laboratory of Sensorimotor Research was elected to membership to the highly prestigious National Academy of Science. Dr. Wurtz's outstanding contributions involve a series of experiments each of which made a pioneering advance in its area. He pioneered the use of conscious monkeys in the study of the visual and oculomotor systems. Years ago, he developed a technique which allows the visual system to be studied in conscious behaving animals and this technique is now a standard technique used throughout the world. Using this technique, Dr. Wurtz was the first to record single cells in the visual cortex of the awake monkey and thus to confirm in awake behaving monkeys the organization of cells in the anesthetized, paralyzed animals seen by Hubel and Wiesel to whom the Nobel Prize was given a few years ago. He went on to analyze the effect of eye movements on visual processing by single cells in the visual pathway. Dr. Wurtz was the first to study the mid-brain structure, the superior colliculus, which is one of the major destinations of the neurons leaving the retina of the eye, and he first determined that the cells in this structure were involved in both vision and eye movements. Dr. Wurtz was also the first to explore the relationship of the basal ganglia to the initiation of the eye movements.

Throughout this work, Dr. Wurtz has combined behavioral analysis, physiological techniques, and histological controls to carry out the most sophisticated experiments possible. He and his associates introduced the use of on-line computers in the analysis of physiological function in a trained behaving animal. In all these experiments Dr. Wurtz has emphasized the functional approach to the nervous system, that is, how brain cells are organized to produce behavior. This in turn has allowed the ready application of the discoveries in the basic research laboratory to deficits seen in man in the clinic. It is this aspect that allows his laboratory within the National Eye Institute to be so closely associated with the clinic and to hold such promise for scientific breakthroughs directly relevant to the understanding of disease. His methodological contributions to the electrophysiological study of vision and oculomotor functions in awake, behaving monkeys are world renowned.

Dr. Chader, Chief of the Laboratory of Retinal Cell and Molecular Biology, won the 1988 Friedenwald Award given by the Association for Research in Vision and Ophthalmology. Dr. Chader won acclaim for studies on two important hereditary diseases of the retina, retinitis pigmentosa and retinoblastoma.

Retinitis pigmentosa is a hereditary blinding disease that selectively strikes the photoreceptor cells of the retina. Dr. Chader's work has linked

abnormalities in cGMP metabolism to retinal degeneration in several animal models of the human disease. In particular, he pinpointed a deficit in cGMP-PDE activity in retinal photoreceptors in the early postnatal period well before the morphological signs of the disease become apparent. This seems to be of general significance since such deficits have now been observed in four RP animal models. Although suitable human retinal RP tissue has not yet been available, this work forms the basis for studies on the human disease and also as a model for other possible diseases in which there is abnormal cyclic nucleotide metabolism.

Dr. Chader has focused on a novel protein that his laboratory first described in the retina in 1976, and has now been named the Interphotoreceptor Retinoid-Binding Protein, (IRBP). This retinoid-binding protein appears to be found only in the eye; it is synthesized by the retina but is quickly secreted into the subretinal space between the retinal photoreceptors and the adjacent pigment epithelial (PE) cell layer. Since vitamin A is stored in PE cell but is utilized in the photoreceptor cell for visual process, it is probable that this protein functions as an extracellular vehicle for retinoid transport between the two tissues. In fact, IRBP has many of the characteristics one would expect of such a transport vehicle including differential retinoid-binding in light and in dark. The protein having been isolated and fully characterized has been cloned in his laboratory. Dr. Chader and associates demonstrated that IRBP is capable of causing experimental autoimmune uveitis (EAU), a feature previously undescribed. Monkeys were found highly susceptible to IRBP-induced EAU. This monkey disease is of special interest because of the close pathological similarity to certain ocular diseases in man, in particular sympathetic ophthalmia and Vogt-Koyanagi-Harada disease. In addition to providing a useful model for the human diseases, the findings with IRBP-induced EAU in monkeys support the notion that autoimmune processes to retinal antigens participate in the etiology of certain human eye diseases.

Laboratory of Mechanisms of Ocular Diseases

Dr. J. Samuel Zigler, Jr., Head of the Cataract Research Section, has received a $50,000 award from the Alcon Research Institute.

Dr. Zigler's pioneering work has been on the mechanisms that account for the oxidative damage occurring in lens undergoing cataract formation. In the case of senile nuclear cataracts, which are characterized by extensive oxidation of crystallins in the lens nucleus, Dr. Zigler was the first to show the possible role of singlet oxygen which is generated photodynamically within the lens. Exposure of crystallins to singlet oxygen produced oxidation of cysteine and tryptophan residues, the formation of non-disulfide covalent crosslinks, the generation of an unusual non-tryptophan fluorescence, increased pigmentation, and aggregation of the proteins. All of these modifications closely resemble changes observed in crystallins from aging and cataractous human lenses.

Cortical cataracts occur in the outer portion of the lens and may result from damage to cell membranes leading to osmotic swelling with consequent cataract formation. Dr. Zigler has investigated the roles of activated states of oxygen in such processes. Using a lens organ culture technique, he has investigated lens membrane damage produced by various "oxygen radical" generating systems. Exposure of lenses in vitro to concentrations of H_2O_2 higher than those to which the lens is normally exposed in vivo, leads to

impaired ability of the lenses to maintain normal cation balance which results in osmotic swelling and loss of transparency.

The situation is quite different when activated species of oxygen are generated within the lens cells rather than in the surrounding fluids. Using solutions of lens proteins as a model of the intracellular environment, Dr. Zigler found that H_2O_2 alone produced little or no structural modifications to the crystallins. On the other hand when conditions were imposed to promote conversion of H_2O_2 into hydroxyl free radical, the crystallins were found to be rapidly modified. The modifications included covalent crosslink formation, increased non-tryptophan fluorescence, aggregation, and changes in the net charge of the polypeptides. Thus the capacity for damage from the various oxygen radicals depends upon the environment. Within the cell the highly reactive hydroxyl free radical is extremely toxic since it is produced in the immediate vicinity of numerous target molecules. When generated outside the lens the stable species, H_2O_2, is most damaging because it can diffuse across cell membranes. After entering the lens fibers the H_2O_2 likely interacts with metal ions, perhaps at specific metal binding sites on proteins, to generate hydroxyl free radical or related species which produce the actual protein damage.

Although the research activities of these three scientists are undoubtedly outstanding, there are other research studies ongoing in an intramural program equally as exciting and important as one will glean by perusing this year's Annual Report.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00065-11 OSD

PERIOD COVERED

October 1, 1987, to September 30, 1988

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

Physiological studies of the Primate Visual System

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

PI: Francisco M. de Monasterio, M.D., D.Sc. Medical Officer OSD, NEI

Others:

COOPERATING UNITS *(if any)*

LAB/BRANCH

Office of the Scientific Director

SECTION

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.55	0.55	0.00

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

The project involves the study of the physiological organization of neurons of the visual system of primates. Studies were carried out to characterize: (1) the chromatic organization of the peripheral region of the "center-surround" organization of the receptive field of color-opponent ganglion cells, and (2) the degree of heterogeneity of properties among color-opponent ganglion cells whose receptive fields are located in the retinal periphery. During the period covered, analyses of some prior studies were completed, and results are being prepared for publication.

(1) Comparison of the results of area-threshold measurements and of chromatic mapping of the receptive field with a small test spot showed that a fraction of the color-opponent ganglion cells of macaque retina has antagonistic center and surround responses mediated in part by the same type of cone mechanism. The apparent frequency of these cells increases towards the retinal periphery, and their resulting center-surround organization provides a simple and direct model for the development of the recently reported "modified Type II" neurons of the striate cortex of macaques.

(2) Further studies of the degree of homogeneity of peripheral color-opponent ganglion cells are consistent with the existence of two main cell classes that differ in terms of conduction velocity, receptive-field center size, and degree of surround antagonism. Preliminary results suggest that some cells of one of these groups loose color-opponent properties in the far periphery, developing a chromatic organization similar to that of the color non-opponent, broad-band ganglion cells.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00122-08 OSD

PERIOD COVERED

October 1, 1987, to September 30, 1988

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

Anatomical Studies of the Primate Visual System

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

PI: Francisco M. de Monasterio, M.D., D.Sc. Medical Officer OSD, NEI

Other:

COOPERATING UNITS *(if any)*

Department of Ophthalmology, Georgetown University, DC (JC Horton, LR Dagi)
Department of Ophthalmology, University of Washington, Seattle (A Bunt-Mylans)

LAB/BRANCH

Office of the Scientific Director

SECTION

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.45	0.45	0.0

CHECK APPROPRIATE BOX(ES)

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

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

This project involves the study of the anatomical properties and organization of cells in the visual system of primates, with emphasis on the retina and the visual cortex. Studies were carried out to characterize (1) the eye-dominance column pattern of human visual striate cortex, (2) the correlation between the staining of blue-sensitive cones by anti-blue cones antibodies and by tissue-reactive dyes, and (3) the reported variability of cone density in the foveal region.

(1) Despite the fact that the striate cortex of humans and macaques differ not only in terms of surface area, but also sulcal and gyral topography, cytochrome oxidase staining shows that the layout of the eye-dominance columns of striate cortex in patients who suffered monocular eye loss before death is very similar to that of macaques. These results indicate that the above anatomical factors do not determine the general pattern of eye-dominance columns.

(2) Preliminary results of the comparison of the staining of a cone population by tissue-reactive dyes, and the labeling of blue-sensitive cones by anti-blue cone antibodies suggest that the putative identification of this population as blue-sensitive cones is indeed correct.

(3) Results from cone density measurements in the fovea and area centralis of the retina of macaque and donor human eyes fail to substantiate, so far, major individual differences in cone density that have been claimed in some studies.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 EY 00135-16

PERIOD COVERED

October 1, 1987 to September 30, 1988

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) OSD, NEI

COOPERATING UNITS *(if any)*

Veterinary Resources Branch, DRS, NIH

LAB/BRANCH

Office of the Scientific Director, NEI

SECTION

INSTITUTE AND LOCATION

National Eye Institute, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.3	1.0	0.3

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

The effects of nutrition, oxidation, and other environmental factors (light intensity or darkness) on the incidence and progress of posterior subcapsular opacities (PSO) associated with retinal degeneration are being studied in Royal College of Surgeons (RCS) rats, in which rod photoreceptor outer segment debris accumulates secondary to a phagocytic defect in the retinal pigmented epithelium. Evidence has been obtained that oxidative changes in polyunsaturated fatty acids in the debris lead to water-soluble toxic aldehydes that can be detected in the vitreous, and are toxic to lens cells and their membranes. Pink-eyed RCS dystrophic rats fed a natural ingredient diet (NIH-07) are highly sensitive to retinal light damage, beginning at light levels as low as 1-4 footcandles, and 27% of such rats develop mature cataracts by 7-12 months. Increased intensity of light (either cyclic or constant) increased the percentage of rats with mature cataracts, while dark rearing from birth prevented the PSO and mature cataracts. Recently, we have found that a purified diet (AIN-76A) fortified with 0.4% beta-carotene + 0.01% BHT also prevented the PSO and mature cataracts. Rhosopsin bleaching appears to be essential for retinal light damage and for initiation of the PSO. A hypothesis has been developed that would explain these findings. It depends upon the known capacity of retinaldehyde to act as a photosensitizer to generate singlet oxygen, an extremely energetic oxidant for polyunsaturated lipids, as well as proteins. Darkness would prevent release of retinaldehyde, while beta-carotene is a direct physical quencher of singlet oxygen, and BHT a highly efficient scavenger for secondary oxidized products. Principles established with the RCS rat model may have significance for slowing or preventing human PSO and mature cataracts, such as those seen in retinitis pigmentosa.

ANNUAL REPORT
NATIONAL EYE INSTITUTE
October 1, 1987 - September 30, 1988

REPORT OF THE CLINICAL DIRECTOR

Robert B. Nussenblatt, M.D.

The Clinical Branch consists of two Sections, each with its own Section Head: Section on Ophthalmic Genetics and Pediatric Ophthalmology, Muriel I. Kaiser-Kupfer, M.D.and the Section on Retinal and Vitreal Diseases, Robert B. Nussenblatt, M.D. (Acting).

The Section on Ophthalmic Genetics and Pediatric Ophthalmology was active in a wide range of activities. One area of major interest was the anterior segment. The short and long-term effects of contact lens wear on the cornea is actively being investigated. The changes in corneal curvature in corneal epithelium morphology as well as endothelial cell morphology that may be induced with long term contact lens wear has great import for many individuals who use this method for correction of vision. Additionally, the group has developed objective and subjective methods to monitor and document opacities in the human lens using different systems. Reproducibility studies on objective systems include the use of the Scheimpflug cameras, the Retroillumination camera, Specular microscope and the laser light-scattering spectroscope. Other systems such as ultrastenography and nuclear magnetic residents (imaging) are being actively tested. The group is finding that it will be necessary to combine subjective and objective methods to characterize adequately the presence, progression or regression of cataracts. Many of the subjective methods that show promise include contrast sensitivity, potential acuity, glare, as well as a well-done visual acuity test.

The group has been extremely interested in the posterior segment as well. The molecular genetics of retinal degenerations has been an area of particular interest. The intent is to identify the genes responsible for different inherited retinal disorders in animal models with the attempt to establish the genetic relationship of these animal disorders to forms of human retinal degenerations. Work has centered on the rd and rds mutations in the mouse and the Abyssinian cat. The hope will be once the molecular basis of one or more of these animal models have inherited and retinal degenerations have been established, that this information will be applied to the human situation. With that in mind, the group has actively participated in the inter-institute medical genetics program and the genetics clinic. During the last year, approximately 400 individuals were seen representing approximately 100 different disease categories. Because of the high frequency of ocular involvement in many of these cases, almost all of the patients were evaluated by the ophthalmic genetics staff or were discussed in consultation. The assessment of the posterior segment degenerative disorders is of upmost important and the group has actively pursued this goal. Objective measurements using electrophysiology techniques has demonstrated a wide variety of observations. Of note is the value of electroretinography in the early diagnosis of progressive cone dystrophy which was studied in a large

number of three generations of a pedigree with dominant progressive cone dystrophy. The use of extensive testing has demonstrated that even at an early age in subjects from families with this disorder, while phychophysical and ophthalmoscopic criteria were insufficient to determine whether they were affected or not, the cone mediated ERG was clearly abnormal. It would certainly appear that until a genetic screening method becomes available the ERG is the earliest indicator of the presence of a cone dystrophy. Studies in gyrate atrophy of the choroid and retina continue. The continued accumulation of natural history data as well as the definition of the genetic abnormalities of this disorder provides us with continued important information in this area. A double-masked controlled randomized clinical trial of topical cysteamine has enrolled 16 patients. These individuals have been enrolled to test the efficacy of topical cysteamine (0.1% in humans) in order to see whether this will prevent the ocular manifestations of this disorder. Most specifically, the collection of crystals in the cornea. Four patients have shown a significant decrease in the cysteamine treated eyes and are now taking drops in both eyes. Recent work has demonstrated that the concentration of cysteamine could be increased to 0.5% with the results of this new dosage still awaited.

The Section on Retinal Diseases and Vitreous remained heavily involved with two long clinical trials. The use of oral sorbinil, an aldose reductase inhibitor, continued to be tested in a randomized masked trial to see if it will inhibit diabetic retinopathy. This study was conducted simultaneously in ten research centers in the United States. Recruitment into this study has stopped and the results of the study will be awaited with great interest. Additionally, patients with macular degeneration continued to be studied in a randomized masked fashion in order to test the efficacy of vitamin E and C therapy as well as the prevention of damage from light below 500 nanometers in preventing this degenerative process. This is the leading cause of newly registered blindness in the white adult population in the United Sates. The recruited patients are examined at four month intervals with a follow-up to continue for five years unless an early beneficial or detrimental effect causes the study to be terminated in less than that time. Testing includes sterio fundus photographs of each macula once a year with the endpoint for the study that of visual acuity of 20/100 or less in the initially better eye because of disc form or atrophic degeneration of the macula. This study will continue until the needed number of patients have been recruited. Additionally, the section has been involved in the study of diabetic patients using vitreous fluorophotometry. Those without retinopathy, those with nonproliferative retinopathy, and normal volunteers have been studied. A new method for evaluating blood retinal barrier permeability to fluorescein and the diffusivity of fluorescein into the vitreous has been developed.

The Clinical Branch reflects new horizons with basic research observations playing an increasingly greater role in the research being conducted.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 EY 00162-06 CB

PERIOD COVERED
October 1, 1987 to September 30, 1988

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

PRINCIPAL INVESTIGATOR *(List other professional personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*
PI: Monique S. Roy M.D. Visiting Scientist CB, NEI

COOPERATING UNITS *(if any)*
Peter Bungay Ph.D. BEIB, NIH

LAB/BRANCH
Clinical Branch

SECTION
Section on Retinal and Vitreal Diseases

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.4	0.4	0

CHECK APPROPRIATE BOX(ES)
☒ (a) Human subjects ☐ (b) Human tissues ☐ (c) Neither
☐ (a1) Minors
☐ (a2) Interviews

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

Vitreous fluorophotometry has been performed in patients with diabetes mellitus without retinopathy, patients with diabetes mellitus with nonproliferative retinopathy, and normal volunteer subjects, age- and sex-matched to the patients. A new method for evaluating blood retinal barrier permeability to fluorescein and diffusivity of fluorescein in the vitreous has been developed. The amount of fluorescein leakage into the vitreous of patients has been 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 other complications were sought.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 EY 00198-05 CB

PERIOD COVERED

October 1, 1987 to September 30, 1988

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

Sorbinil Retinopathy Trial

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

PI:	Monique S. Roy	M.D.	Visiting Scientist	CB, NEI
Others:	Manuel Datiles	M.D.	Staff Ophthalmologist	CB, NEI
	James R. Carl	M.D.	Senior Staff Fellow	CB, NEI

COOPERATING UNITS *(if any)*

R. Silverman — NIDDK, NIH

LAB/BRANCH

Clinical Branch

SECTION

Section on Retinal and Vitreal Diseases

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.7	0.7	0

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

Oral sorbinil, an aldose reductase inhibitor, will be administered in a double-masked randomized trial to diabetics with no or minimal diabetic retinopathy. This will be done to evaluate the effects of sorbinil on the development of diabetic retinopathy and further investigate the safety and toleration of sorbinil. The study will be conducted simultaneously in 10 research centers in the USA.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 EY 00187-05-CB

PERIOD COVERED
October 1, 1987 to September 30, 1988

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:	Lessie McCain	R.N.	Clinical Technician	CB, NEI
	Kayoko Kashima	M.D.	Visiting Associate	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:
.15	0.10	.05

CHECK APPROPRIATE BOX(ES)

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

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

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 risk involved to corneal tissues, and how a systemic or local disorder may increase these risks.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 EY 00188-05 CB

PERIOD COVERED

October 1, 1987 to September 30, 1988

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:	Robert Sperduto	M.D.	Head, Epidemiology Branch	BEP, NEI
	Peter Kador	Ph.D.	Head, Section on Molecular Pharmacology	LMOD, NEI
	Lessie McCain	R.N.	Clinical Technician	CB, NEI

COOPERATING UNITS *(if any)*

Image Processing and Analysis Laboratory, DCRT, NIH (Benes Trus, Ph.D., Chief)
Clinical and Diagnostic Trials Section, NCI, NIH (Sylvan Green, M.D.)
Nuclear Medicine, Clinical Center, NIH (Joseph Frank, M.D.)

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:
1.2	1.2	

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

We are developing objective and subjective methods to monitor and document opacities in the human lens using different systems. We are presently actively recruiting patients with and without cataracts for reproducibility studies on the objective systems--the Scheimpflug cameras (Zeiss and topcon), Retroillumination camera (Neitz), Specular microscope (Keeler) and laser light-scattering spectroscope (KOWA). We will also test other systems using sound (ultrasonography), and nuclear magnetic resonance (magnetic resonance imaging). We are also studying subjective systems or methods, such as the effects of cataracts on visual perception, contrast sensitivity, and glare, which may be useful as additional parameters in the monitoring of cataract presence, progression, or regression.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00212-03 CB

PERIOD COVERED

October 1, 1987 to September 30, 1988

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
	Muriel I. Kaiser-Kupfer	M.D.	Head, Section on Ophthalmic Genetics and Pediatric Ophthalmology	CB, NEI

COOPERATING UNITS *(if any)*

Jin H. Kinoshita	Ph.D.	Scientific Director	NEI
W. Gerald Robison, Jr.	Ph.D.	Head, Section on Pathophysiology	LMOD, NEI

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:
0.85	0.85	

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

There is presently an extreme scarcity 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 intraocular lens. We are exploring ways by which fragmented lens materials can be maximally used in cataract basic research through close collaboration with cataract surgeons and basic researchers and modification of techniques by both groups.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 EY 00246-01 CB

PERIOD COVERED
October 1, 1987 to September 30, 1988

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

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

PI:	Michael B. Gorin	M.D., Ph.D.	Medical Officer	CB, NEI
Others:	Ignacio Rodriguez	Ph.D.	Staff Fellow	CB, NEI

COOPERATING UNITS *(if any)*
Northwestern University (Larry Pinto, Ph.D.), University of Linkoping, Linkoping, Sweden (Kristina Narfstrom) National Cancer Institute, (Stephen O'Brien, Ph.D., Chief, LVC, DCE, NCI)

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:
1.9	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.)*

The purpose of this project is to identify the genes responsible for different inherited retinal disorders in animal models and to establish the genetic relationship of these animal disorders to forms of human retinal degenerations.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00011-14 CB

PERIOD COVERED

October 1, 1987 to September 30, 1988

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

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:
0.25	.15	.2

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

The purpose of this project is to determine the risks of patient with pigment dispersion syndrome to develping glaucoma. Comparisons of patients with and without glaucoma will be mde based on diagnostic tests, genetic screening, aqueous humor dynamics and pupillary responses to light. The data acquired may enable a determination of the risk of patients with pigment dispersion syndrome to developing glaucoma as well as add to the understanding of the pathology of the disease.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 EY 00062-12 CB

PERIOD COVERED
October 1, 1987 to September 30, 1988

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 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.25	.15	.1

CHECK APPROPRIATE BOX(ES)

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

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

This project was formerly titled "Progressive Essential Iris Atrophy." Patients are being recruited with progressive essential iris atrophy 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

PROJECT NUMBER

Z01 EY 00083-11 CB

PERIOD COVERED

October 1, 1987 to September 30, 1988

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

Gyrate Atrophy of the Choroid and Retina and Other Retinal Degenerations

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:	Michael Gorin	M.D., Ph.D.	Medical Officer	CB, NEI
	Lessie McCain	R.N.	Clinical Technician	CB, NEI
	Rafael Caruso	M.D.	Visiting Scientist	CB, NEI
	Doris Collie	A.A.	Health Technician	CB, NEI

COOPERATING UNITS *(if any)*

The Howard Hughes Medical Institute Laboratory and the Department of Pediatrics, Johns Hopkins University, School of Medicine, Baltimore, Maryland (David L. Valle, M.D.)

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:
1.2	0.7	0.5

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

Patients with gyrate atrophy of the choroid and retina are examined systematically to confirm the diagnosis. Skin fibroblats 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 00163-06 CB

PERIOD COVERED

October 1, 1987 to September 30, 1988

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:	Michael B. Gorin	M.D., Ph.D.	Medical Officer	CB, NEI
	Lessie McCain	R.N.	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 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
.2	.1	.1

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

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 diseases. During the last year, approximately 400 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

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 EY 00172-06 CB

PERIOD COVERED
October 1, 1997 to September 30, 1998

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

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	CB,NEI
Others:	Carl Kupfer	M.D.	Director	NEI
	Monique S. Roy	M.D.	Visiting Scientist	CB,NEI

COOPERATING UNITS *(if any)*
None

LAB/BRANCH
Clinical Branch

SECTION
Section on Ophthalmic Genetics and Pediatric Ophthalmology

INSTITUTE AND LOCATION
NIH, NEI, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.2		

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

This study will determine if patients with severe visual loss because of age related 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 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

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 EY 00123-08-CB

PERIOD COVERED
October 1, 1987 to September 30, 1988

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

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:	Rafael C. Caruso	M.D.	Visiting Scientist	CB, NEI
	Kent E. Higgins	Ph.D.	Expert	CB, NEI
	Ralph D. Gunkel	O.D.	Ophthalmic Physicist	CB, NEI

COOPERATING UNITS *(if any)*
Georgetown University Center for Sight, Washington, D.C. (Despina Koutsandreas, O.T., Robert Toma, C.O.T.)

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:
1.3	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 visual function of patients with ocular diseases or lesions in the visual pathways and of normal subjects is measured with psychophysical techniques. These data are correlated with those obtained with electrophysiological tests of visual function. The results obtained contribute to the diagnosis of ocular and neural disorders that affect vision, and are needed to characterize their nature and evolution. They are also valuable in the assessment of the effect of treatment regimens on the outcome of these diseases.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00144-07-CB

PERIOD COVERED

October 1, 1987 to September 30, 1988

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

Clinical Electrophysiology of the Visual System

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:	Rafael Caruso	M.D.	Visiting Scientist	CB, NEI
	Doris J. Collie	A.A.	Health Technician	CB, NEI

COOPERATING UNITS *(if any)*

Georgetown University Center for Sight, Washington, D.C. (Despina Koustsandreas, O.T., Robert Toma, C.O.T.)

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:
.60	.30	.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 visual function of patients with ocular diseases or lesions in the visual pathways and of normal subjects is measured objectively with electrophysiological techniques. These data are correlated with those obtained with psychophysical tests of visual function. The results obtained contribute to the diagnosis of ocular and neural disorders that affect vision, and are needed to characterize their nature and evolution. They are also valuable in the assessment of the effects of different forms of treatment on the outcome of these diseases.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00211-03 CB

PERIOD COVERED

October 1, 1987 to September 30, 1988

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

A Double-Masked Controlled Randomized Clinical Trial of Topical Cysteamine

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
	Manuel Datiles	M.D.	Visiting Scientist	CB, NEI

COOPERATING UNITS *(if any)*

Human Genetics Branch, NICHD, National Institutes of Health, Bethesda, Maryland (William Gahl, M.D., Ph.D.)

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:
.25	.15	.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.)*

Nephropathic cystinosis is an autosomal, recessively inherited storage disease in which nonprotein cystine accumulates within cellular lysosomes due to a defect in lysosomal cystine transport. Ocular manifestations include photophobia crystal deposits in cornea, conjunctiva, iris and depigmentation of the retina. Systemic complications include the Fanconi syndrome, and renal failure.

Eight years ago cysteamine, a free thiol which depletes cystine from cells, was introduced in the therapy of cystinotic patients. Although patients had improved growth and stabilized renal function, there was no noticeable effect on the accumulation of corneal crystals. Recent studies showed that corneal cells in tissue culture are readily depleted of cystine by the introduction of cysteamine, making feasible the use of topical ophthalmic cysteamine to circumvent the humoral route. After appropriate animal studies to test for complications which revealed none, we have begun a double-masked clinical trial to test the efficacy of topical cysteamine (0.1%) in humans. Sixteen patients have thus far been enrolled. Four patients have shown significant decrease in the cysteamine treated eyes and are now taking drops in both eyes. To permit increasing the concentration of cysteamine eye drops in humans, a study was performed in rabbits, permitting an increase in the concentration to 0.5%.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00060-10 CB

PERIOD COVERED
October 1, 1987 to September 30, 1988

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.	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:
.65	.15	.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 with 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 00084-10 CB

PERIOD COVERED
October 1, 1987 to September 30, 1988

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
	Paul Edwards	M.D.	Visiting Fellow	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:
0.75	0.55	.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.)*

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.

ANNUAL REPORT
NATIONAL EYE INSTITUTE
October 1, 1987 - September 30, 1988

REPORT OF THE CHIEF, LABORATORY OF IMMUNOLOGY

Robert B. Nussenblatt, M.D.

This was the third year for the Laboratory of Immunology, National Eye Institute. While the first year saw the establishment of four Sections within the Laboratory, each with its own Section Head, the end of the second year brought into the Laboratory a new Section, that of Molecular Biology. Therefore, at present the Laboratory's five Section Heads are: Section on Clinical Immunology, Alan G. Palestine, M.D., Section on Immunology and Virology, John J. Hooks, Ph.D., Section on Experimental Immunology, Igal Gery, Ph.D., Section of Molecular Biology, Toshimichi Shinohara, Ph.D., and Section on Immunoregulation, Robert B. Nussenblatt, M.D.

Over the past year the Section on Clinical Immunology has been particularly interested in the question of possible autoimmunity to the anterior uvea in patients with uveitis. Though many forms of anterior uveitis are presumed to be due to autoimmunity, there has been no confirmation that an ocular specific antigen is indeed involved in this process. Patients with anterior uveitis have been screened for autoantibodies directly against bovine iris and antibodies have been detected in some patients to a protein with a molecular weight of approximately 22,000. This protein appears to be specific to the iris, and further studies are continuing in order to illustrate what might be the first identification of such an antigen in the anterior segment of the eye. Additionally, the section has been actively involved in the role of the neuro-endocrine axis on the immune response. While the section has previously shown that the use of bromocriptine, a prolactin inhibitor, can modulate S-antigen induced experimental autoimmune uveitis, this work has been carried into the human sphere. The results of a double-masked study using bromocriptine alone in an attempt to reduce the number of recurrent attacks of anterior uveitis demonstrated that there was no major difference between groups receiving this drug as opposed to placebo. Additionally, a second trial focuses on the additive effects of cyclosporine plus bromocriptine in an attempt to treat patients with posterior uveitis at lower dosages of cyclosporine in order to reduce its concurrent renal toxicity. These results continue to be collected with the very important evaluation of renal function to be done in the not too distant future. As well, the section has developed a variety of techniques to evaluate the role of the retinal vasculature in ocular inflammatory disease. This includes the growing of vascular endothelial cells as well as newer ways to evaluate the vasculature in vivo.

The Section on Experimental Immunology has been actively involved in learning the pathogenesis of inflammatory eye diseases. They have concentrated particularly on the model for uveitis induced with ocular specific antigens. The focus of the past year has recently been on the interphotoreceptor retinoid-binding protein (IRBP) which is highly uveitogenic and produces experimental autoimmune uveitis (EAU) in various animals including primates. The focus has been on the identification of peptide determinants of IRBP that are responsible for inducing EAU and initiating

immune responses. Some 14 peptides selected for synthesis from the IRBP sequence have been looked at and 4 peptides were found to be uveitogenic in Lewis rats. One of the peptides designated R14 was shown to be extremely potent in inducing disease at a dose as low as 0.06 micrograms per rat. Additionally, this protein as well as a second designated R4 were also found to produce EAU in primates. This work will be expanded over the ensuing year to evaluate the peptides from IRBP to which patients with severe inflammatory disease of the eye may respond.

The Section of Molecular Biology over the past year has concentrated on the question of molecular mimicry as well determining the amino acid sequences of human, mouse and bovine S-antigen. Immunogenic sites, as well as uveitopathogenic sites, have been identified in this molecule. As with the IRBP molecule, EAU as well as pinealitis can be induced in Lewis rats with small peptides. Of interest, the disease can also be induced with a small peptide corresponding to the amino acid positions 106-117 in the yeast histone H3 which contains five consecutive amino acids identical to a uveitogenic pathogenic site in the human S-antigen. This potential cross-reactivity may provide us with future insight into basis mechanisms of cross-reactivity and molecular mimicry in the future.

The Section on Immunology and Virology has continued to develop its interest into several areas including T-cell modulators. The development of virally induced diseases and also the study on the bioregulatory aspects of the retinal pigment epithelial (RPE) cell. The group has successfully modulated the expression of experimentally induced uveitis with the treatment of animals with anti-Ia therapy. Additionally, studies continue on the expression of class II antigens localized in autoimmune diseases both in human tissue as well as in the animal system. The presence of class II molecules on retinal blastoma cells has also been demonstrated. The modulation of HLA-DR by gamma-interferon as well as the preferential expression of this determinant over HLA-DQ has also been shown. Of interest, double labeling studies have revealed that the HLA-DR antigen is shared concomitantly with cells of glial and neuronal character. The area of the retinal pigment epithelial cell has developed considerably over the past year. The group has identified two mouse IgG monoclonal antibodies which react with the human RPE cell. These monoclonal antibodies are both specific for the RPE cell within the eye and do not appear to react with any other ocular structures. Additionally, they do not react with human skin, kidney or peripheral mononuclear cells. These antibodies recognize cell surface molecules which are highly conserved since they can be found in not only man but also in monkey, rat, mouse, cow, chicken and frog. These are the first monoclonal antibodies which are directed solely at the human RPE cell. Additionally, the group has initiated studies to evaluate corona virus infections in the eye and optic nerve. These preliminary studies have begun with hope that these will come to fruition over the ensuing year.

The Section on Immunoregulation has been evaluating the role of cytokines in human intraocular fluids. Intraocular fluids from patients who require surgery to repair a retinal detachment or surgery due to sequelae of uveitis have been evaluated. These patients' fluids were evaluated for the presence of interleukin-1 as well as interleukin-2 activity by bioassays. Ten percent

of uveitis patients, 20% of retinal detachment patients and 60% of patients with proliferative vitreal retinopathy (PVR) had detectable IL-2 activity. Of great interest was the fact that IL-1 activity was found in 90% of uveitic eyes, 35% of eyes with retinal detachment and 17% of eyes with proliferative vitreal retinopathy. IL-1 would seem to be a mediator in multiple organ specific pathways. Further, its presence in the eye suggests a role in intraocular inflammatory and immune processes and as well in ocular diseases that are not usually associated with the immune system. Of great interest was the relatively high percentage of PVR patients with IL-2 activity thus suggesting a role of the immune system in this proliferative vitreal retinopathy. The group has additionally begun the use of a new antibiotic, magainin. Preliminary studies in this area have demonstrated in vivo activity of magainin by showing a less severe corneal abscess in the treated animals with the delayed onset of the abscess as compared to the control animals. This important area will be continued over the ensuing year. The group has also used a molecular biologically prepared IL-1 linked to the exotoxin of pseudomonas. This novel approach has permitted the group to pinpoint cells that bear IL-2 receptors (such as activited clones that will be mediating uveitis) and destroy them. This experimental approach appears to be successful and will be looked at in greater detail over the ensuing year. Additionally, the mouse model of experimental autoimmune uveitis has been well developed and the development of long term cell lines as well as clones will be an important goal over the ensuing year. The therapeutic intervention in human intraocular inflammatory disease took an important step in the initiation of a phase 1/2 randomized trial using cyclosporine A and G. This study has great import in that cyclosporine G may be considerably less nephrotoxic and therefore may be a reasonable next generation immunosuppressive agent.

The Laboratory of Immunology's Sections have produced significant observations over this past year, both clinically as well as from a basic research point of view. The goal for all is a better understanding of the basic mechanisms of ocular inflammatory diseases. This work will continue with this fabric of basic research combined with practical observations such as the treatment of patients with cyclosporine as well as other immunomodulating agents.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00230-03 LI

PERIOD COVERED
October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Modulation of Retinal Vascular Permeability by Inflammatory Mediators

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

PI:	Alan G. Palestine	M.D.	Head, Section on Clinical Immunology	LI, NEI
Others:	Rebecca Gurley	M.S.	Biologist	LI, NEI
	David C. Herman	M.D.	Senior Staff Fellow	LI, NEI
	Jeffrey N. Bloom	M.D.	Senior Staff Fellow	LI, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Immunology

SECTION
Section on Clinical Immunology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.83	0.43	0.4

CHECK APPROPRIATE BOX(ES)

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

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

Retinal vascular leakage is an important mechanism of visual loss in ocular inflammatory disease. The presumed site of retinal vascular leakage is the retinal capillaries which are composed of pericytes and endothelial cells. Therefore, it is likely that immune mediated disease alters pericyte or endothelial function in a manner that produces vascular leakage. This project is concerned with quantifying the specific mediators that are involved in producing these changes so that more appropriate therapy can be targeted.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00217-03 LI

PERIOD COVERED
October 1, 1987 to September 30, 1988

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.	Head, Section on Clinical Immunology	LI, NEI
Others:	Robert B. Nussenblatt	M.D.	Clinical Director	NEI
	Jeffrey N. Bloom	M.D.	Senior Staff Fellow	LI, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Immunology

SECTION
Section on Clinical Immunology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.26	0.26	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.)*

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 disease can also be transferred using a T-helper cell line by intra-peritoneal or intra-ocular injection. 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 or blood 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. Cells from an S-Ag specific T cell line migrate into the retina and cause EAU. The kinetics of this migration are being studied. S-antigen specific cells reach the eye in greater numbers if the inflammation in the eye is induced by S-antigen than if it is induced by another mechanism.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00218-03 LI

PERIOD COVERED
October 1, 1987 to September 30, 1988

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

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

PI:	Alan G. Palestine	M.D.	Head, Section on Clinical Immunology	LI, NEI
Others:	Robert B. Nussenblatt	M.D.	Clinical Director	NEI

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

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INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.09	0.09	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.)*

Cytomegalovirus retinitis is the major cause of blindness in AIDS patients. Although we have previously shown that ganciclovir is effective in treating this infection, the disease relapses without continued maintenance. Maintenance therapy requires intravenous infusion and is associated with marrow toxicity. A multi-center randomized trial is currently being planned to evaluate the use of this drug.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00219-03 LI

PERIOD COVERED

October 1, 1987 to September 30, 1988

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

The Effect of Bromocriptine on Human Uveitis

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

PI:	Alan G. Palestine	M.D.	Head, Section on Clinical Immunology	LI, NEI
Others:	Robert B. Nussenblatt	M.D.	Clinical Director	NEI
	Janet L. Davis	M.D.	Senior Staff Fellow	LI, NEI
	David C. Herman	M.D.	Senior Staff Fellow	LI, NEI
	Jeffrey N. Bloom	M.D.	Senior Staff Fellow	LI, NEI

COOPERATING UNITS *(if any)*

Metabolism Branch, National Cancer Institute (Marie C. Gelato, M.D.)

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TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.91	0.91	0

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

In recent years there has been increasing evidence in the literature that pituitary hormones are capable of regulating the immune system. There is evidence to suggest that prolactin is an immunostimulatory hormone and that reduction of serum prolactin levels in experimental animals by hypothesectomy or treatment with bromocriptine will result in a degree of immunosuppression.

This information has been applied to humans and two clinical studies have begun. Both of these are in early phase of patient recruitment. One study is a randomized trial between placebo and bromocriptine in recurrent anterior uveitis using the end point of the number of recurrences per year to determine whether bromocriptine is capable of regulating the immune system in these patients. The second trial focuses on the additive effects of cyclosporine plus bromocriptine in attempts to treat patients with posterior uveitis at lower doses of cyclosporine to reduce its concurrent renal toxicity while at the same time achieve an immunosuppressive effect. Cyclosporine and prolactin compete for binding sites on the lymphocyte.

Further studies in human disease will hopefully elucidate other aspects of the neuroendocrine axis which can be utilized to regulate the immune system to treat autoimmune diseases.

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NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00220-03 LI

PERIOD COVERED
October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Endocrine Modulation of Immune-Mediated Eye Disease in Rats

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

PI:	Alan G. Palestine	M.D.	Head, Section on Clinical Immunology	LI, NEI
Others:	Robert B. Nussenblatt	M.D.	Clinical Director	NEI
	David C. Herman	M.D.	Senior Staff Fellow	LI, NEI

COOPERATING UNITS *(if any)*

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NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.31	0.31	0

CHECK APPROPRIATE BOX(ES)

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

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

In recent years there has been increasing evidence in the literature that hormones are capable of regulating the immune system. There is evidence to suggest that prolactin is an immunostimulatory hormone and that reduction of serum prolactin levels in experimental animals by hypothesectomy or treatment with bromocriptine will result in a degree of immunosuppression.

An animal model of experimental autoimmune uveitis (EAU) induced by immunization of rats with S-antigen (a soluble antigen from the retina) is used to study intraocular inflammatory disease. We have demonstrated a decrease in antibody production in both male and female rats and a decreased incidence of uveitis in female animals but no significant effect on the immune responses measured by lymphocyte proliferation. As reported before, high doses of cyclosporine (10 mg/kg) results in only partial reduction of intraocular inflammation. We have demonstrated that the suppression of prolactin by concurrent use of bromocriptine in combination with low dose cyclosporine is more effective than either drug separately in suppressing both the incidence of disease as well as cellular and humoral immune responses. Evidence in the literature suggests that cyclosporine competes with prolactin for binding sites on lymphocytes therefore reductions in prolactin level may reduce competition for those sites and make cyclosporine treatment more effective. Further studies with this animal model will elucidate other aspects of the neuroendocrine axis that may be utilized to regulate the immune system to treat autoimmune diseases.

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NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00221-03 LI

PERIOD COVERED
October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Intraocular Class II Antigen Expression in Endotoxin-Induced Uveitis

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

PI:	Alan G. Palestine	M.D.	Head, Section on Clinical Immunology	LI, NEI
Others:	Robert B. Nussenblatt	M.D.	Clinical Director	NEI
	Jeffrey N. Bloom	M.D.	Senior Staff Fellow	LI, NEI
	David C. Herman	M.D.	Senior Staff Fellow	LI, NEI

COOPERATING UNITS *(if any)*

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TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.51	0.51	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.)*

Endotoxin is a polysaccharide derived from the cell wall of gram negative bacteria. When injected into the footpad or the eye of a rat it will induce an inflammatory reaction within the eye. The mechanism of this inflammation is still unclear. However, since several types of anterior uveitis in humans appear to be linked to gram negative bacteria exposure, this is considered a relative model for anterior uveitis in humans such as Reiter's syndrome. In this study the expression of class II antigens was studied within the eyes of rats receiving E. coli endotoxin by immunohistochemical techniques. We observed that the expression of class II antigens on the ciliary body and iris preceeded the influx of inflammatory cells into the eye and that the inflammatory cells that entered the eye were primarily neutrophils with some monocytes. No T-cells were present in the inflammatory infiltrate. The inflammatory cellular infiltrate could be inhibited by indomethacin or colchicine, however this did not alter the expression of class II antigens by the iris or ciliary body indicating that this expression is not simply a consequence of the inflammatory infiltrate but may be intimately involved with the mechanism of the expression of endotoxin induced uveitis. Corticosteroids were capable of suppressing both the cellular inflammatory infiltrate and the expression of class II antigens. The expression of class II antigens on nonlymphoid cells within the eye may be important in antigen presentation or may simply signal a phenotypic change on the cells due to the interaction of endotoxin with the cell membranes. The findings were compared with the expression of class II antigen in passive and active intraocular Arthus. The effect of endotoxin on ocular inflammation was studied using fluorophotometry to validate the use of animal studies as a useful

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NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00247-01 LI

PERIOD COVERED
October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Autoimmunity to the Anterior Uvea in Patients with Uveitis

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

PI:	Alan G. Palestine	M.D.	Head, Section on Clinical Immunology	LI, NEI
Others:	Rebecca Gurley	M.S.	Biologist	LI, NEI

COOPERATING UNITS *(If any)*

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TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.77	0.17	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.)*

Many forms of anterior uveitis are presumed to be due to autoimmunity directed towards ocular antigens. However, there has been no confirmation that an ocular specific antigen is involved in this process. It is important to develop an understanding of the mechanisms of inflammation in patients that have anterior uveitis. The presumed site of inflammation in these patients is the iris and ciliary body. We, therefore, began to look for iris specific proteins to which patients might have an autoimmune response. Patients with anterior uveitis were screened for auto-antibodies directed against bovine iris. Antibodies were detected to a protein with a molecular weight of approximately 22,000 in some patients. When compared to a control group, patients, in general, have higher levels than control individuals of this antibody. Until the protein is isolated and T-cell responses can be measured, the true significance of these antibodies will be unclear. Antibodies to retinal antigens are much less revealing than the corresponding T-cell responses in distinguishing patients from controls. The protein that has been identified appears to be specific to the iris and is not found in other tissues of the body. Purification of this protein for other immunologic studies is in progress.

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NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00069-11 LI

PERIOD COVERED
October 1, 1987 to September 30, 1988

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	LI, NEI
Others:	Shigeto Hirose	M.D.	Visiting Fellow	LI, NEI
	Hiroki Sanui	M.D.	Visiting Associate	LI, NEI
	Takao Tanaka	M.D.	Visiting Fellow	LI, NEI
	LiHong Hu	M.D.	Visiting Fellow	LI, NEI
	Satoshi Kotake	M.D.	Visiting Fellow	LI, NEI

COOPERATING UNITS *(if any)*

Stephen I. Katz	M.D.		DB, NCI, NIH
Hanah Margalit	Ph.D.		LMB, NCI, NIH
Horst W. Korf		University of Geissen, FRG	

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TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
7.83	7.43	0.4

CHECK APPROPRIATE BOX(ES)

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

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

This project is aimed at learning about the pathogenesis of inflammatory eye diseases which are grouped under the term "uveitis". As a model for uveitis in man we have induced "experimental autoimmune uveoretinitis" (EAU) in experimental animals by immunization with ocular-specific antigens. We have recently shown that a retinal component, the interphotoreceptor retinoid-binding protein (IRBP) is highly uveitogenic and produces EAU in various animals, including primates. Our main effort in FY-1988 has focused on the identification of peptide determinants of IRBP that are responsible for inducing EAU and initiating immune responses. Of the fourteen peptides selected for synthesis from the IRBP sequence, four peptides were found to induce EAU in Lewis rats. One of the peptides, designated R14, was extremely potent, inducing disease at a dose as low as 0.06 μg/rat; the other three peptides were approximately 1000 fold less active. A correlation was found between the capacity of the peptides to induce EAU and to initiate cellular immunity which cross reacts with the native IRBP molecule. Two peptides, R4 and R14, were also found to produce EAU in primates, thus suggesting that these peptides could be involved in human uveitic conditions as well.

In other studies we have collected data to suggest the possible involvement of non-MHC-restricted killer lymphocytes ("NK" and "LAK") and of interferon-γ (IFN-γ) in the pathogenesis of EAU. A marked increase in the non-MHC-restricted cytotoxic activity was observed in monkeys immunized for induction of EAU. Treatment of mice with IFN-γ significantly elevated the expression of Ia (class II) antigens on various ocular cells, with a pattern resembling that seen in animals which develop EAU.

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NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00232-03 LI

PERIOD COVERED
October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Interferon System in Cellular Function and Disease

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

PI:	John J. Hooks	Ph.D.	Head, Section on Immunology and Virology	LI, NEI
Others:	Barbara Detrick	Ph.D.	Expert	LI, NEI
	Caroline Percopo	B.S.	Biologist	LI, NEI
	Christian Hamel	M.D.	Visiting Fellow	LI, NEI
	Muriel Kaiser-Kupfer	M.D.	Head, Section on Ophthalmic Genetics	CB, NEI

COOPERATING UNITS *(if any)*

Jan Vilcek	M.D.	New York University, School of Medicine	
Charles Evans	M.D.	Head, Tumor Biology Section	LB, NCI

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TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.1	0.7	0.4

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

The interferon (IFN) proteins can modify a variety of biological activities and are considered one of the body's regulatory proteins. Numerous studies now indicate that the IFN's are potent immunoregulators. During the past year we have been studying the ways in which IFN proteins interact with cells of the immune system and how this interaction may modify immune responses and immunologically related disorders.

Using immunocytochemical analysis we have developed a sensitive method of identifying lymphokines, IFN-gamma and IL2, at the site of tissue damage. We have identified these lymphokines in inflammatory eye diseases. The presence of these lymphokines is associated with a lymphocyte infiltrate predominantly of a T-cell origin and with the expression of MHC class II antigens on both the infiltrating cells and in the retinal pigment epithelial (rpe) cells.

Experimentally we have shown that this direct intravitreal inoculation of recombinant rat IFN-γ results in the expression of MHC Class II antigen (Ia) in a variety of ocular cells.

This is the first demonstration of lymphokines, IFN-gamma and IL2 at the site of a localized autoimmune disease. These observations may indicate that IFN-gamma induced MHC class II antigen expression may serve as a local amplification system in autoimmune and inflammatory eye disease. A better understanding of the role of lymphokines in the mechanisms involved in the development of autoimmunity and inflammation may be beneficial in the treatment of these diseases.

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NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00233-03 LI

PERIOD COVERED

October 1, 1987 to September 30, 1988

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

Studies on the Bioregulatory Aspects of the Retinal Pigment Epithelial Cell

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

PI:	John J. Hooks	Ph.D.	Head, Section on Immunology and Virology	LI, NEI
Others:	Barbara Detrick	Ph.D.	Expert	LI, NEI
	Caroline Percopo	B.S.	Biologist	LI, NEI
	Susan Robbins	Ph.D.	Postdoctoral Fellow	LI, NEI
	Laura Caspers-Velu	M.D.	Visiting Associate	LMOD, NEI
	Shuji Suzuki	M.D.	Visiting Associate	LI, NEI

COOPERATING UNITS *(if any)*

	Lawrence Bowsell	M.D.	Hopital St. Louis, France
	Alain Bernard	M.D.	Institute Gustave Rowsse, France
	Reuben Siraganian	M.D.	NIDR, NIH

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TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.96	1.76	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 retinal pigment epithelial (rpe) cell is a major regulatory cell in the eye. That is, the rpe cell exerts a variety of actions in maintaining retinal integrity and function. In order to more effectively study this cell in vivo and in vitro, we have produced monoclonal antibodies directed against human rpe cells.

Using immunoperoxidase assays (ABC), we have identified two mouse IgG monoclonal antibodies which react with the human rpe cell. The monoclonal antibodies are both specific for the rpe cell within the eye, since they do not react with any other ocular structures. Moreover, these antibodies do not cross react with human skin, kidney or peripheral mononuclear cells. These antibodies recognize cell surface molecules which are highly conserved since they can be found in man, monkey, rat, mouse, cow, chicken and frog.

These are the first monoclonal antibodies which are directed solely at the human rpe cell. Further characterization and studies with this antibody should prove useful in the identification of rpe cells in situ and in vitro. Moreover, this immunoglobulin will allow us to probe the bioregulatory functions of the cell.

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NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00234-03 LI

PERIOD COVERED
October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
MHC Class II Antigens in the Pathogenesis of Inflammatory Diseases

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

PI:	John J. Hooks	Ph.D.	Head, Section on Immunology and Virology	LI, NEI
Others:	Barbara Detrick	Ph.D.	Expert	LI, NEI
	Caroline Percopo	B.S.	Biologist	LI, NEI
	Chi-Chao Chan	M.D.	Medical Officer	LI, NEI
	Robert B. Nussenblatt	M.D.	Clinical Director	NEI

COOPERATING UNITS *(if any)*

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NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.40	0.30	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.)*

MHC class II antigens, HLA-DR in the human and Ia in the mouse, are membrane bound glycoproteins that are encoded by genes of the major histocompatibility complex. Expression of these antigens is of great functional importance for the initiation and perpetuation of immune responses. In a number of immunopathologic conditions HLA-DR antigen negative cells are stimulated to express class II antigens. In these cases an immunologic role has been postulated for the class II antigen expression.

During the past year, we have determined if class II antigens are expressed in certain diseases as well as evaluated their possible role in autoimmune and inflammatory diseases. Initial studies identified cells in the anterior segment and cells in the retina (rpe cell) which express class II antigens during inflammatory eye diseases. Treatment with monoclonal anti-Ia antibodies diminished the clinical disease and the expression of MHC class II antigens.

These studies on MHC class II antigen expression in localized autoimmune diseases provide evidence that the activation of these antigens may contribute to the immunopathogenesis of these diseases.

GPO 914-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00240-02 LI

PERIOD COVERED
October 1, 1987 to September 30, 1988

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

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

PI:	John J. Hooks	Ph.D.	Head, Section on Immunology and Virology	LI, NEI
Others:	Susan Robbins	Ph.D.	Postdoctoral Fellow	LI, NEI
	Christian Hamel	M.D.	Visiting Fellow	LI, NEI
	Barbara Detrick	Ph.D.	Expert	LI, NEI
	Caroline Percopo	B.S.	Biologist	LI, NEI
	Robert B. Nussenblatt	M.D.	Clinical Director	NEI

COOPERATING UNITS *(if any)*
See attached

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TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.00	0.90	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.)*

During the past year we have initiated studies to evaluate the various virologic and immunopathologic processes which occur when viruses replicate in the ocular microenvironment. This is a new project which is composed of three areas: (1) Evaluation of virus spread in HSV-1 induced retinitis. (2) Studies on coronavirus infection in ocular and optic nerve cells. (3) Determination of possible role of other viruses in human eye diseases.

Retinitis following anterior chamber inoculation of herpes simplex virus (HSV-1) is an interesting model of viral spread and virus induced disease. During the past year we have elucidated some of the pathologic mechanisms involved in this disease. We found that footprints of the immune system (IFN-gamma and MHC class II antigen expression) can be identified in the protected retina strongly indicating that it is the immune system which protects the retina from virus destruction. Moreover, we identified the virus in the capillary body and ciliary nerves suggesting that this may be the mode of spread of the virus to the uninjected eye. Elucidation of virus spread and activation in the retina may provide insight into these same mechanisms in human disease, such as acute retinal necrosis.

We have initiated studies to evaluate coronavirus infections in the eye and optic nerve. Monoclonal anti-virus receptor antibody has identified selected cells within the eye which express virus receptors. Preliminary studies indicate that the virus is capable of inducing ocular damage in the posterior pole.

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NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00184-06 LI

PERIOD COVERED
October 1, 1987 to September 30, 1988

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

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

PI:	Rachel R. Caspi	Ph.D.	Visiting Associate	LI, NEI
Others:	Robert B. Nussenblatt	M.D.	Clinical Director	NEI
	Francois Roberge	M.D.	Visiting Associate	LI, NEI
	Chi-Chao Chan	M.D.	Medical Officer	LI, NEI
	William Leake	M.S.	Biologist	LI, NEI
	Makoto Higuchi	M.D.	Visiting Fellow	LI, NEI

COOPERATING UNITS *(if any)*

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TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.06	2.02	0.04

CHECK APPROPRIATE BOX(ES)

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

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

Cellular mechanisms of ocular immunologically-mediated disease are being studied in animal models of experimental autoimmune uveoretinitis. For this purpose, previously established models are used (eg, S-Ag uveitis in the Lewis rat) and new models are being developed (IRBP and S-Ag uveitis in different strains of mice). In vivo-functional long-term T-cell lines and T-cell clones are developed and maintained in vitro from lymphoid organs of experimental animals immunized with uveitogenic ocular proteins. The phenotype and functional properties of these cells, as well as their interaction with ocular resident cells are being studied. The goal of these studies will be to identify the immunoreactive cells and mediators involved in the intraocular inflammatory process.

GPO 814-918

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00222-03 LI

PERIOD COVERED
October 1, 1987 to September 30, 1988

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

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

PI:	Chi-Chao Chan	M.D.	Medical Officer	LI, NEI
Others:	Robert B. Nussenblatt	M.D.	Clinical Director	NEI
	Igal Gery	Ph.D.	Head, Section on Experimental Immunology	LI, NEI
	Rachel R. Caspi	Ph.D.	Visiting Associate	LI, NEI
	Francois Roberge	M.D.	Visiting Associate	LI, NEI

COOPERATING UNITS *(if any)*
University of Tokyo, School of Medicine (Manabu Mochizuki, M.D.)

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Laboratory of Immunology

SECTION
Section on Immunoregulation

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.31	0.31	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.)*

Identity and topographic localization of immunocompetent cells and alteration of surface markers on ocular resident cells in rodents with experimental autoimmune uveoretinitis by active immunization or adoptive transfer were analyzed by immunohistochemical studies. The lymphocyte population at the inflammatory sites was found to change markedly during the course of disease. In the early stage, T-helper/inducers are the predominant cells in the eye. A relative increase of T-suppressor/cytotoxic cells in the late stage were observed. Expression of major histocompatibility complex class II antigens on ocular resident cells such as RPE, retinal endothelium, keratocytes, fibroblast and ciliary epithelium was observed in different models of EAU in rats. This antigen expression may play a certain role in the pathogenesis of EAU. Both infiltrating (cell subpopulation) and expression of class II antigens on ocular resident cells, can be modulated by different immunosuppressive agents.

Dynamics of EAU induced by adoptive transfer of S-antigen-specific T-lymphocyte cell line has showed that this cell line can recognize the photoreceptor S-Ag in vivo. Immunopathology in the eyes with EAU in mice can be presented as a chronic granulomatous inflammation. Development of subretinal neovascularization may occur. Expression of major histocompatibility complex class II antigens is only located on ocular resident cells with the presence of inflammatory cells.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00224-03 LI

PERIOD COVERED
October 1, 1987 to September 30, 1988

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

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

PI:	Chi-Chao Chan	M.D.	Medical Officer	LI, NEI
Others:	Robert B. Nussenblatt	M.D.	Clinical Director	NEI
	Alan G. Palestine	M.D.	Head, Section on Clinical Immunology	LI, NEI
	Toichiro Kuwabara	M.D.	Head, Laboratory of Ophthalmic Pathology	LOP, NEI

COOPERATING UNITS *(if any)*

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Laboratory of Immunology

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Section on Immunoregulation

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.12	0.12	0

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

Immunocompetent cells and ocular resident cells in the ocular tissues from patients with a clinical diagnosis of sympathetic ophthalmia were examined using the immunohistochemical technique. The choroidal infiltrates were composed primarily of T-lymphocytes. Different amounts of macrophages and B lymphocytes were present in each case. A varied spectrum of immunopathological and histopathological findings may occur in clinically diagnosed sympathetic ophthalmia. The immunopathology resembles EAU induced by retinal soluble model. Exposure of uveal tissue outside the eye and adjuvant effect may be important in the pathogenesis of this disease in humans.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00225-03 LI

PERIOD COVERED

October 1, 1987 to September 30, 1988

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

Post-Inflammatory Complications in Uveitis

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

PI:	Chi-Chao Chan	M.D.	Medical Officer	LI, NEI
Others:	Robert B. Nussenblatt	M.D.	Clinical Director	NEI
	Francois Roberge	M.D.	Visiting Associate	LI, NEI

COOPERATING UNITS *(if any)*

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Section on Immunoregulation

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.12	0.12	0

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

Complications of post-inflammation in uveitis patients includes destruction of photoreceptors, gliosis, choroidal scar, and formations of cyclitic membrane, snowbanking and preretinal membrane. Pos-inflammatory membrane composition may play an important role in the cause of complications associated with uveitis. In this study, eyes enucleated from patients with end stages of chronic anterior uveitis (formation of cyclitic membrane), pars planitis (formation of preretinal membrane) were evaluated immunohistochemically. Glial cells and proliferating Müller cells were the major cellular components in these membranes. Basement membrane-like components and new collagens were the major extracellular membrane components.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00226-03 LI

PERIOD COVERED
October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Immunopathology of Ocular Onchocerciasis and Other Parasitic Diseases

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

PI:	Chi-Chao Chan	M.D.	Medical Officer	LI, NEI
Others:	Robert B. Nussenblatt	M.D.	Clinical Director	NEI

COOPERATING UNITS *(if any)*
National Institute of Allergy and Infectious Diseases, Clinical Parasitic Diseases Section (Eric A. Ottesen, M.D.); World Health Organization (K. Awadzi, M.D.)

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Laboratory of Immunology

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Section on Immunoregulation

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.33	0.33	0

CHECK APPROPRIATE BOX(ES)

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

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

Ocular specimens and sera from 12 patients with onchocerciasis and 10 controls were studied. A mild to moderate chronic inflammatory cellular infiltration was present in the conjunctiva of the onchocerciasis patients. T-lymphocytes were the predominant inflammatory cells with the T-suppressor subset being significantly increased in the onchocerciasis patients when compared to controls. In the onchocerciasis patients, the nonlymphoid cells in the conjunctiva and iris, such as vascular endothelia, pericytes and fibroblasts, showed an increase in expression of class II antigens. The anti-Onchocerca volvulus antibodies in the sera and aqueous humor were significantly higher in the patients compared to the controls. These findings suggest that T-cells are important in the ocular immune response to Onchocerca and that expression of class II antigens on nonlymphoid cells and the humoral factors may all play a critical role in ocular onchocerciasis.

Retinal auto-antibodies in sera of these 12 patients were found. They were bound to the inner retinal layer and photoreceptors. Such autoimmune antibodies may play a role in the pathogenesis of the retinal degeneration and optic atrophy that occurs as a consequence of onchocerciasis.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00241-02 LI

PERIOD COVERED
October 1, 1987 to September 30, 1988

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

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

PI:	Chi-Chao Chan	M.D.	Medical Officer	LI, NEI
Others:	Robert B. Nussenblatt	M.D.	Clinical Director	NEI
	Alan G. Palestine	M.D.	Head, Section on Clinical Immunology	LI, NEI
	Ming Ni	M.D.	Visiting Fellow	LI, NEI
	Toichiro Kuwabara	M.D.	Head, Laboratory of Ophthalmic Pathology	CB, NEi

COOPERATING UNITS *(if any)* Zhongshan Ophthalmic Center, Guangzhon, Chine (Winifred Mao, M.D.); University of Iowa (Jay H. Frachmer, M.D.); Georgetown University Center for Sight (Michael Lemp, M.D.)

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Laboratory of Immunology

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Section on Immunoregulation

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.27	0.27	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.)*

Ocular specimens from human ocular tissues with various diseases, such as uveitis, conjunctival and corneal diseases, and ocular metabolic genetic diseases were studied using immunoperoxidase technique as well as light and electron microscopic evaluation. In uveitis, immunocompetent cells and lymphokines are critical in the reflection of clinical diagnosis, disease course and prognosis. In non-uveitis, alteration of cellular membrane surface markers and intracytoskeleton on the ocular resident cells may imply damages and abnormalities in these diseases.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00231-03 LI

PERIOD COVERED
October 1, 1987 to September 30, 1988

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

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

PI:	Barbara Detrick	Ph.D.	Expert	LI, NEI
Others:	John J. Hooks	Ph.D.	Head, Section on Immunology and Virology	LI, NEI
	Gerald J. Chader	Ph.D.	Chief	LRCMB, NEI
	Caroline Percopo	B.S.	Biologist	LI, NEI

COOPERATING UNITS *(if any)*

Charles Evans	M.D.	Head, Tumor Biology Section	LB, NCI
Norman Katz	M.D.	Walter Reed Army Medical Center	
Merlyn Rodrigues	M.D.	University of Maryland, Baltimore	

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INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.6	0.4	0.2

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

Retinoblastoma (Rb), an ocular tumor of childhood, consists of multipotent embryonic cells that have the potential to differentiate into neuronal or glial-like components. MHC class II antigens (HLA-DR, DQ, DP) are integral glycoproteins which are critical elements in immune regulation. The identification of these determinants on a variety of primitive stem cell types and tumor cells arrested at selected phases of their cell cycle has suggested that these molecules play a role in cellular differentiation.

Recently, we demonstrated the presence of the class II molecules on Rb cells. In addition, the modulation of HLA-DR by IFN-γ as well as the preferential expression of this determinant over HLA-DQ is described. Double labeling experiments revealed that HLA-DR antigen is shared concomitantly with cells of glial and neuronal character.

Based on these initial studies, additional investigations are in progress. One approach focuses on the correlation of class II antigen expression with cellular differentiation. A second examines the prognostic significance of these molecules on retinoblastoma cells and the possible relationship these proteins may have to the modulation and management of this tumor. Finally, a third study will examine the role of IFN-gamma as a differentiating agent of this tumor.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00235-03 LI

PERIOD COVERED
October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Identification and Modulation of Class II Antigens

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

PI:	Barbara Detrick	Ph.D.	Expert	LI, NEI
Others:	John J. Hooks	Ph.D.	Head, Section on Immunology and Virology	LI, NEI
	Chi-Chao Chan	M.D.	Medical Officer	LI, NEI
	Caroline Percopo	B.S.	Biologist	LI, NEI
	Robert B. Nussenblatt	M.D.	Clinical Director	NEI

COOPERATING UNITS *(if any)*

G. Aguirre	D.D.S., P.D.	Univ. of Pennsylvania
Barton F. Haynes	M.D.	Duke University
Laurence Boumsell	M.D.	Paris, France

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SECTION
Section on Immunology and Virology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.44	0.34	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.)*

Class II antigens are integral glycoproteins encoded by genes in the major histocompatibility complex. Their expression is critical to immune reactivity. Although most immune cells constitutively express class II antigens, some non-immune cell types can be induced to demonstrate these molecules under selected conditions, such as an immunologic or degenerative event. Based on our earlier data, demonstrating that retinitis pigmentosa patients had an alteration in IFN-gamma production and class II antigen expression, we expanded our studies to evaluate class II antigen expression in a variety of ocular situations. We found that the retinal pigment epithelium cell does not express class II antigen in the normal eye. In contrast, the rpe cell did express these molecules in a retinal degenerative disorder (retinitis pigmentosa) and in two ocular inflammatory diseases (sympathetic ophthalmia and uveitis). Using the EAU animal model of ocular autoimmune disease we demonstrated that the rpe cell is activated to express class II antigens prior to clinical and histopathological evidence of the disease. Finally, we demonstrated that EAU could be altered with anti-Ia therapy. In this study EAU animals receiving monoclonal anti-Ia antibodies experience not only less ocular inflammation but also a delay in the onset of EAU. Moreover, immunocytochemistry analysis revealed that eyes from these animals expressed less Ia antigen as well as a diminution of infiltrating macrophages and lymphocytes. These data show that anti-Ia treatment significantly modifies the course of EAU in the rat. We have also demonstrated that direct inoculation of recombinant IFN-gamma results in the expression of MHC class II (Ia) in a variety of ocular cells. We are continuing to investigate the effects of other potent modulators with the hope that an alteration in activation or expression of these molecules may modify the disease process to the benefit of the host.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00092-10 LI

PERIOD COVERED

October 1, 1987 to September 30, 1988

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. Clinical Director NEI

COOPERATING UNITS *(if any)*

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Laboratory of Immunology

SECTION

Section on Immunoregulation

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.03	0.03	0

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

Patients with 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. Restriction fragment analysis has begun to complement these HLA studies.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: Z01 EY 00075-10 LI

PERIOD COVERED
October 1, 1987 to September 30, 1988

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.	Clinical Director	NEI
Others:	Alan G. Palestine	M.D.	Head, Section on Clinical Immunology	LI, NEI
	William Leake	M.S.	Biologist	LI, NEI
	Rashid Mahdi		Biologist	LI, NEI
	Janet L. Davis	M.D.	Senior Staff Fellow	LI, NEI

COOPERATING UNITS *(If any)*

LAB/BRANCH
Laboratory of Immunology

SECTION
Section on Immunoregulation

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.60	0.40	1.2

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

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, purified uveitogenic soluble antigen (S-antigen), IRBP of the retina, and uveitogenic fractions of the retinal S-antigen are being used in a lymphocyte microculture technique to evaluate the presence of cellular immune memory to ocular tissues. In addition, purified antigens from the toxoplasmosis organism are also being tested in this in vitro system. 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 which may shed light on the basic mechanisms of uveitis and may be used as a guide for specific immunologic therapy. The serum from these patients is also being evaluated. Using retinal biopsy, a new retinopathy in AIDS appears to have been identified.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00094-10 LI

PERIOD COVERED

October 1, 1987 to September 30, 1988

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.	Clinical Director	NEI
Others:	Phuc Le Hoang	M.D.	Visiting Scientist	LI, NEI
	Rashid Mahdi		Biologist	LI, NEI

COOPERATING UNITS *(if any)*

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Section on Immunoregulation

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.)*

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. The cyclosporines, a family of drugs with specific anti-T-cell-activity, have been found to be exceptionally effective in protecting rats with EAU. Attempts at local immunosuppressive therapy in order to prevent EAU have begun. Topical and periocular cyclosporine-A (CsA) have been used in order to evaluate its effectiveness in EAU. Newer cyclosporines, particularly D&G, have been evaluated in this model, with their efficacy compared to that of CsA. Ciamexone, a drug with immunopotentiating characteristics, has always been utilized in this model. The use of "natural" immunomodulatory models are being developed.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00115-08 LI

PERIOD COVERED

October 1, 1987 to September 30, 1988

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.	Clinical Director	NEI
Others:	Alan G. Palestine	M.D.	Head, Section on Clinical Immunology	LI, NEI
	Janet L. Davis	M.D.	Senior Staff Fellow	LI, NEI
	Jeffrey N. Bloom	M.D.	Senior Staff Fellow	LI, NEI
	David C. Herman	M.D.	Senior Staff Fellow	LI, NEI
	Chi-Chao Chan	M.D.	Medical Officer	LI, NEI

COOPERATING UNITS *(if any)*

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Laboratory of Immunology

SECTION

Section on Immunoregulation

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.75	0.75	0

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

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. A phase I/II randomized trial using Cyclosporine A and G has begun.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00228-03 LI

PERIOD COVERED

October 1, 1987 to September 30, 1988

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.	Visiting Associate	LI, NEI
Others:	Robert B. Nussenblatt	M.D.	Clinical Director	NEI
	Rachel Caspi	Ph.D.	Visiting Associate	LI, NEI

COOPERATING UNITS *(if any)*

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Section on Immunoregulation

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NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.92	0.92	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 work extended our ongoing study of interactions between the retinal glial Müller cell and T-lymphocytes. In an in vitro co-culture system, Müller cells had been shown to exert a profound inhibitory influence on the proliferation of T-helper cell lines through a membrane bound factor. Investigations of the nature of the inhibitory moiety revealed that it was sensitive to proteinase. Further studies showed that the expression of the factor on the surface of Müller cells could be suppressed by glucocorticoids.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00249-01

PERIOD COVERED

October 1, 1987 to September 30, 1988

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

Cytokines in Human Intraocular Fluids

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

PI:	Janet L. Davis	M.D.	Senior Staff Fellow	LI, NEI
Others:	Robert B. Nussenblatt	M.D.	Clinical Director	NEI

COOPERATING UNITS *(if any)* Eye Research Institute, Boston, Massachusetts (Alex E. Jalkh, M.D.); Eye Research Institute, Boston, Massachusetts (Charles Schepens, M.D.); University of Miami, Miami, Florida (Harry W. Flynn, Jr., M.D.)

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NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.32	0.32	0

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

Human intraocular fluids are collected during the course of surgery to repair retinal detachment, remove vitreous and strip membranes of proliferative vitreoretinopathy (PVR), and remove vitreous and cataract from uveitic eyes. These fluids (ordinarily discarded) are analyzed for interleukin 1 (IL-1) and interleukin 2 (IL-2) activity by bioassays. Specimens from 88 patients have been analyzed for IL-1. Il-1 activity was found in 90% of uveitic eyes, 35% of eyes with retinal detachment and 17% of eyes with proliferative vitreoretinopathy. Thirty-two specimens have been analyzed for IL-2. Ten percent of uveitis patients, 20% of retinal detachment patients and 60% of PVR patients had detectable IL-2 activity. IL-1 is a mediator in multiple organ-specific pathways. Its presence in the eye suggests a role in intraocular inflammatory and immune processes. IL-2 is produced by activated T cells. The high percentage of PVR patients with IL-2 activity suggests a role of the immune system in proliferative vitreoretinopathy.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00248-01

PERIOD COVERED

October 1, 1987 to September 30, 1988

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

Magainin Therapy of Infectious Keratitis

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

PI:	Phuc Le Hoang	M.D.	Visiting Scientist	LI, NEI
Others:	Robert B. Nussenblatt	M.D.	Clinical Director	NEI
	Janet L. Davis	M.D.	Senior Staff Fellow	LI, NEI
	Rashid Mahdi		Biologist	LI, NEI

COOPERATING UNITS *(if any)*

Human Genetics, National Institute of Child Health and Human Development (Michael Zasloff, M.D., Ph.D.); Human Genetics, National Institute of Child Health and Human Development (Charles Bevins, M.D., Ph.D.)

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Laboratory of Immunology

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Section on Immunoregulation

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.5	1.0	0.5

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

Studies in animals are being carried out to determine the in vivo activity of a new class of antimicrobial peptides isolated from the skin of the African frog Xenopus laevis and called magainins. This family of peptides consists of two closely related peptides that are each 23 amino acids which inhibit growth of numerous species of bacteria and fungi in vitro. An animal model of experimental bacterial keratitis induced in adult New Zealand white rabbits was used to determine the in vivo relevance of the antimicrobial activity of magainins. Pseudomonas aeruginosa corneal infection was primarily considered because it is the most destructive and the most difficult to treat corneal infection in humans. Each cornea was infected by an intrastromal injection of 100 bacteria. The topical treatment with magainin drops or ocular ointment was started either 4 hours or 20 hours after the infection. The control animals were either not treated or treated with the vehicle (PBS or petrolatum plus mineral oil). These preliminary studies demonstrated the in vivo activity of the magainin by showing a less severe corneal abscess in the treated animals with a delayed onset of the abscess as compared to the control animals. Although the animals could tolerate well the treatment, magainin drops and ointment induced a chemosis with a conjunctival hyperhemia by themselves which can aggravate the conjunctival inflammation related to the infection.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00132-07 LI

PERIOD COVERED

October 1, 1987 to September 30, 1988

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

Molecular Biology of Phototransduction

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

PI:	Toshimichi Shinohara	Ph.D.	Head, Section on Molecular Biology	LI, NEI
Others:	Masahiko Tsuda	M.D., Ph.D.	Visiting Associate	LI, NEI
	Benjamin Amaladoss	Ph.D.	Visiting Associate	LI, NEI
	Kunihiko Yamaki	M.D., Ph.D.	Visiting Associate	LI, NEI
	Charles Egwuagu	Ph.D.	Staff Fellow	LI, NEI
	Shuji Suzuki	M.D., Ph.D.	Visiting Associate	LI, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Immunology

SECTION

Section on Molecular Biology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.13	4.13	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 eye has a remarkable property in that it can function efficiently over a very wide range of illuminations from single photon to bright sun. The rod cells which have photosensitive rhodopsin are more sensitive to dim light and dark adapts to increase their sensitivity. However, the rod cells cease their sensitive phototransduction in bright light, the cone cells are in contrast operative in bright light.

Rhodopsin, transducin, PDE, rhodopsin kinase and S-antigen have been known to be associated with the phototransduction cascade, our focus of interest is on rhodopsin kinase and S-antigen. In order to further understand this light dependent modulatory mechanism in rod outer segments, we have characterized S-antigen, rhodopsin kinase, calmodulin and 24K ROS specific proteins using recombinant DNA technologies. S-antigen had local regions of sequence homology with α-transducin including the putative rhodopsin binding and phosphoryl binding sites.

Rhodopsin kinase is a family of proteins which have conserved features and similar catalytic domains among themselves. Also, calmodulin is a family of Ca^{++} binding proteins and it had conserved domins too. The 24k ROS specific protein did not have any sequence similarity with other known proteins. Thus, the amino acid sequences of these proteins further substantiated the functional roles of these proteins in the phototransduction cascade.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 EY 00250-01 LI

PERIOD COVERED
October 1, 1987 to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Molecular Biology of Experimental Autoimmune Uveitis

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

PI:	Toshimichi Shinohara	Ph.D.	Head, Section on Molecular Biology	LI, NEI
Others:	Kunihiko Yamaki	M.D., Ph.D.	Visiting Associate	LI, NEI
	Vijay K. Singh	Ph.D.	Visiting Associate	LI, NEI
	Charles Egwuagu	Ph.D.	Staff Fellow	LI, NEI
	Tohru Abe	M.D.	Visiting Associate	LI, NEI

COOPERATING UNITS *(if any)*

Larry A. Donoso	M.D., Ph.D.	Wills Eye Hospital, Philadelphia, PA	

LAB/BRANCH
Laboratory of Immunology

SECTION
Section on Molecular Biology

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.2	2.2	0

CHECK APPROPRIATE BOX(ES)

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

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

Inflammatory diseases of the eye are a significant cause of visual handicap in the United States and throughout the world with severe cases often leading to blindness. Autoimmune processes directed against normal eye tissues, such as the retina, are thought to play a significant role in the pathogenesis of such diseases. Molecular mimicry, a process by which an immune response directed against a non-self protein cross reacts with a normal host protein, may play a role in autoimmunity. Experimental autoimmune uveitis (EAU) serves as an animal model of ocular inflammation. The disease is caused by the immunization of microgram amounts of a soluble retinal protein, designated S-antigen, in susceptible animal strains, including primates.

We have determined amino acid sequences of human, mouse and bovine S-antigen. Immunogenic sites and four uveitopathogenic sites using 20 different chemically synthesized oligopeptides were also determined. We induced EAU and pinealitis in Lewis rats with a small synthetic peptide, corresponding to amino positions 106 to 117 in yeast histone H3, which incidentally contains five consecutive amino acids identical to a uveitopathogenic site in human S-antigen. In addition, native yeast histone H3 was also capable of inducing an EAU. These findings provide a basis for autoimmune inflammatory diseases of the eye in humans.

ANNUAL REPORT
NATIONAL EYE INSTITUTE
October 1, 1987 - September 30, 1988

REPORT OF THE CHIEF, LABORATORY OF MECHANISMS AND OCULAR DISEASES

Jin H. Kinoshita, Ph.D.

A quarter of a century ago, Drs. Cogan and Kuwabara introduced the hypothesis that the initiating factor in diabetic retinopathy was the selective loss of the retinal capillary pericytes. Drs. Kador and Akagi thought that the degeneration of the pericytes in diabetes was due to aldose reductase (AR). In order to support their hypothesis, it was essential to demonstrate the presence of AR in pericytes. Where others have failed, Drs. Kador and Akagi demonstrated immunohistochemically that AR was found in the pericytes and not in the endothelial cells of human retinal capillaries. More recently this was confirmed by others in our laboratory who showed that cell cultures of human retinal capillary pericytes do contain AR as demonstrated by biochemical, immunohistochemical, and molecular biological techniques.

Recently Drs. Kador and associates have initiated diabetic retinopathy studies in galactosemic dogs. This model has been shown by Engerman to develop a background retinopathy which was indistinguishable from that of diabetic dogs. Dr. Kador and associates have been following the progression of retinal changes in both AR treated and untreated galactosemic dogs. They found that along with with pericyte ghosts in untreated dogs, there was proliferation of endothelial cells, the presence of acellular capillaries and later microaneurysm formation. All these retinal changes in galactosemic dogs were prevented by treatment with aldose reductase inhibitor.

Similar results were observed in the rat model. Although rats were not known to develop diabetic retinopathic changes, Dr. Robison has recently shown retinal micro-and macrovascular changes in long term galactosemic rats. He also found loss of pericytes, proliferation of endothelial cells and microaneurysms. Different from the galactosemic dogs, were the engorged veins, venules, and capillaries in the retina of galactosemic rats. All these retinal changes in galactosemic rats were prevented by an aldose reductase inhibitor.

These studies emerging from the laboratories of Drs. Kador and Robison are most significant and may pave the way in the development of a new treatment modality for diabetic retinopathy.

Another research area of active progress is the study on gyrate atrophy (GA) in Dr. Inana's laboratory.

Gyrate atrophy is a blinding autosomal recessive degenerative disease of the retina and choroid of the eye characterized by a generalized deficiency of the mitochondrial enzyme, ornithine aminotransferase (OAT). The knowledge of the underlying biochemical defect in GA enabled Dr. Inana to take a molecular genetic approach in studying this disease. First, he constructed and characterized a molecular probe for the human OAT in the form of a cDNA clone. Analysis of the cDNA-derived OAT sequence revealed the presence of an OAT precursor containing a leader sequence similar to those found in other mitochondrial proteins of cytoplasmic origin. A differential hybridization analysis of the human genome using specific OAT cDNA-derived probes demonstrated the presence of one putative functional OAT gene and at least three other OAT-related genes indicating a gene family. The functional OAT and OAT-related gene sequences were mapped to a precise area of chromosones 10 and X. A sequence analysis of OAT gene clones confirmed the chromosone 10 gene to be the functional gene and at least one of the X chromosone genes to be a pseudogene. Analysis of the OAT gene, mRNA, and protein in 20 GA patients using the OAT DNA and antibody probes demonstrated a GA case with a partial heterozygous deletion of the OAT gene, no OAT mRNA, and undectable level of OAT protein. The rest of the cases showed normal OAT gene and variably reduced levels of OAT mRNA and protein. In one of the cases the OAT mRNA level was shown to be half of normal, indicating expression of only one of the OAT gene alleles, and a point mutation was demonstrated in the expressed mRNA resulting in an amino acid change in the OAT protein. The results from these cases constitute the first real demonstration of the molecular genetic defect of OAT present in GA.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00245-01 LMOD

PERIOD COVERED
October 1, 1987 to September 30, 1988

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

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

PI:	Teresa Borrás	Ph.D.	Expert	LMOD, NEI
Others:	Anna Rodokanaki	M.D.	Visiting Fellow	LMOD, NEI

COOPERATING UNITS *(if any)*
Karolinska Institute, Stockholm, Sweden (Dr. Hans Jornvall)
NIADDK, Diabetes Branch (Dr. Flora de Pablo)

LAB/BRANCH
Mechanisms of Ocular Diseases

SECTION
Section of Cataracts

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.8	1.6	0.2

CHECK APPROPRIATE BOX(ES)

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

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

Cataract development is a complex process involving a whole range of different causes. The hereditary cataracts in our animal model provide an excellent opportunity to identify changes in gene regulation that will result in the formation of lens opacity. The study of gene expression changes in hereditary cataract of strain 13/N of guinea pigs is particularly important because it provides the only model of nuclear hereditary cataract and because guinea pigs, as humans, are born with their eyes open, when this cataract is already present.

A new guinea pig lens crystallin, ζ-crystallin, discovered in our section by Drs. Huang-Zigler, appears to be absent or sharply reduced in the lens of the cataractous animal. We set up to clone the copy of the mRNA encoding Zeta-crystallin as a first approach to understand which step of the regulation of this gene could be responsible for the development of the cataract.

We screened a guinea pig cDNA library with a synthetic oligonucleotide and obtained a positive clone (pTB100) of 1448 base pairs (bp). This clone contains the full ζ-protein coding region of 328 amino acids with a MW of 35,071 daltons; it provided us with the first primary structure of this novel protein.

Computer search of the ζ-crystallin sequence in the protein sequence data bank revealed a 33% similarity of this protein with the alcohol dehydrogenase (ADH) protein family. Further analysis of the comparison proved to be statistically significant indicating that ζ-crystallin belongs to the superfamily of the ADHs. The role of this similarity and its significance in lens transparency is under present study.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00201-04 LMOD

PERIOD COVERED

October 1, 1987 to September 30, 1988

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

Molecular Biology of Aldose Reductase

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

PI:	Deborah Carper	Ph.D.	Biologist	LMOD, NEI
Others:	Chihiro Nishimura	M.D.	Visiting Associate	LMOD, NEI
	Caroline Graham	B.A.	Chemist	LMOD, NEI
	Masayuki Kaneko	M.D.	Visiting Associate	LMOD, NEI

COOPERATING UNITS *(if any)*

David J. Barrett, Jules Stein Eye Institute, UCLA, Los Angeles, CA

LAB/BRANCH

Laboratory of Mechanisms of Ocular Diseases

SECTION

Section on Cataracts

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

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

Aldose reductase (AR) of the polyol pathway has been implicated in some of the disabling complications of diabetes. We have now successfully completed the protein sequence for aldose reductase using cDNA sequencing and primer extension analysis of AR mRNA. The primary structure of AR consists of an open reading frame of 948 nucleotides encoding for a 316 amino acid polypeptide (including the initiation methionine) with a molecular weight of 35,797. Secondary structure predictions indicate that AR is over 50% β-Sheet.

Protein comparisons have previously revealed structural relatedness (41% to 57%) among vertebrate aldose reductase, aldehyde reductase, prostaglandin F synthase and the frog lens protein ρ-crystallin. This superfamily can now be extended to prokaryotes by the inclusion of Corynebacterium 2,5 diketo-D-gluconate reductase. This more distantly related protein shares 30-40% identity with the vertebrate enzymes.

Southern blot analysis indicated the existence of a multi-gene family for AR. Since our amino acid sequence data for AR have revealed considerable sequence similarity to other aldo/keto reductases, it will be interesting to elucidate the relationship between genes encoding these proteins and a gene family for AR.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00189-05 LMOD

PERIOD COVERED

October 1, 1987 to September 30, 1988

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

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. Research Chemist LMOD, NEI

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Mechanisms of Ocular Disease

SECTION

Cataracts

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	1.0	0.0

CHECK APPROPRIATE BOX(ES):

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

☐ (a1) Minors

☐ (a2) Interviews

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

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 mechanisms leading to the changes; and 3) the effect of the modifications on structure and function of lens proteins. Bovine and human lenses were used. The approach has been to study the modifications of lens proteins after treatment in vitro by mixed function oxidation systems. Treatment of bovine γ_2-crystallin caused the loss of about two sulfhydryls and a progressive loss of methionine residues with increased time of oxidation. Only a fraction of a cysteic acid residue was found and the modification of other amino acids has not yet been correlated with new species formed upon oxidation. Deamidation has yet to be examined. Similar studies are in progress on a human gamma crystallin expressed in mouse L cells; the goal is to identify the modified amino acids. The proteins of bovine trabecular meshwork extracted by various procedures were analyzed by polyacrylamide gel electrophoresis. The profile was very similar to that of human trabecular meshwork. There were a few significant differences between calf and cow trabecular meshworks. These results suggest that bovine trabecular meshwork may be a useful model system to study glaucoma.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00237-03 LMOD

PERIOD COVERED

October 1, 1987 to September 30, 1988

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

Characterization of the Lens

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

PI:	Paul Russell	Ph.D.	Research Chemist	LMOD, NEI
Others:	Masao Nakamura	M.D.	Visiting Associate	LMOD, NEI

COOPERATING UNITS *(if any)*

Division of Cancer Research, University of Toronto (S. Meakin, M. Breitman, L.-C. Tsui) Howe Laboratory and Harvard University (D.L. Epstein); Lab of Retinal Cell and Molecular Biology, NEI (S. Gentleman)

LAB/BRANCH

Laboratory of Mechanisms of Ocular Diseases

SECTION

Section on Cataract

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.6	1.6	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 processes of aging in the human lens have been difficult to study because the mechanisms by which alterations occur in the lens are not known. The proteins in the lens undergo distinctive changes in their charge but the cause of these modifications and the relationship between these alterations and cataract formation is not established. One way of investigating these changes is to study the individual proteins in vitro and determine how modifications affect the structure and interactions of these crystallin proteins with other proteins. One of the major groups of proteins in the lens is γ-crystallin. One of the γ-crystallin genes has been stably integrated into mouse L-cells. By using the γ-crystallin expressed in the mouse cells, studies of the alteration of the human protein in an oxidation system have been done. The microheterogeneity and the shift of the protein to more acidic forms that are observed in the aging human lens have been observed with the crystallin in vitro. It would appear that the many of the alterations that are seen in the γ-crystallin in the nucleus of the human lens can be mimicked with a mixed function oxidation system on isolated proteins. Thus, many of the changes that have been reported on aging in the human lens may be the result of oxidative damage to the components of the lens.

Additionally, work has progressed on the calcium binding proteins of the lens. These proteins, called annexins, may play a major role in development and differentiation in the lens. At least two of the major calcium binding proteins in the lens have been shown to be glycosylated. The addition of sugar residues on these proteins may indicate there is another level of control which the cell has for these very important proteins.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00105-09 LMOD

PERIOD COVERED

October 1, 1987 to September 30, 1988

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)*

PI:	J. Samuel Zigler, Jr.	Ph.D.	Research Biologist	LMOD, NEI
Others:	Qing-ling Huang	M.D.	Visiting Fellow	LMOD, NEI
	Xinyu Du	M.D.	Visiting Fellow	LMOD, NEI

COOPERATING UNITS *(if any)*

Department of Chemistry, Adelphi University (F. Bettelheim); Department of Ophthalmology, University of Tennessee (H.M. Jernigan, Jr.); Oakland University, Rochester, MI (V.N. Reddy), Alcon Laboratories (M.Lou)

LAB/BRANCH

Laboratory of Mechanisms of Ocular Diseases

SECTION

Section on Cataract

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

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.)*

Lens crystallins are evolutionarily conservative proteins that are the primary structural constituents of the lens. The focus of work in this laboratory is oriented toward: 1) increased understanding of the structural attributes of these proteins which contribute to their fitness to serve as components of a transparent tissue and 2) elucidation of the mechanisms whereby changes in the composition of lens crystallins or aging-related modification of these long-lived proteins can contribute to opacification of the lens.

The studies on zeta-crystallin, a lens protein, thus far found only in guinea pigs, have yielded several significant new findings. We now know that this protein is related to alcohol dehydrogenase and thus apparently represents the first reported example of a taxon-specific crystallin in a mammal in which an enzyme has been adopted by the lens as a structural protein. Since zeta-crystallin is not present in the animals homozygous for the congenital cataract trait, it is possible that the lack of zeta may be the initiating factor in the formation of the cataract. Such a situation would provide a unique system for studying the function of an individual crystallin as part of the transparent protein matrix in the lens. Studies on protein synthesis in the cataract lenses reveal significant synthesis of a protein which is not detected in normal lenses. Use of an antibody raised against a synthetic peptide from zeta-crystallin reveals that this second protein is related to zeta.

It has been demonstrated that both inhibition of the glutathione redox cycle with BCNU or decreasing lens ATP through use of 2-deoxyglucose can potentiate the oxidative modification of crystallins in cultured rat lenses exposed to hydrogen peroxide.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00193-05 LMOD

PERIOD COVERED

October 1, 1987 to September 30, 1988

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.	Section Head	LMOD, NEI
Others:	Carmelann Zintz	Ph.D.	Staff Fellow	LMOD, NEI
	Yoshihiro Hotta	M.D.	Visiting Associate	LMOD, NEI
	Carolynn Chambers	Ph.D.	IRTA Fellow	LMOD, NEI
	Tetsuo Sasabe	M.D., Ph.D.	Visiting Associate	LMOD, NEI
	Keiko Fujiki	Ph.D.	Professional Consultant	LMOD, NEI

COOPERATING UNITS (if any)

See next page

LAB/BRANCH

Laboratory of Mechanisms of Ocular Diseases

SECTION

Molecular Pathology Section

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.4	5.4	0

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

Ornithine Aminotransferase Deficiency in Gyrate Atrophy: Gyrate atrophy (GA) is a blinding, autosomal recessive degenerative disease of the retina and choroid of the eye characterized by a generalized deficiency in the mitochondrial enzyme, ornithine aminotransferase(OAT). Our molecular genetic investigation of this disease has resulted in the cloning and characterization of a cDNA for the human OAT, mapping of the OAT gene sequences to chromosomes 10 and X, identification of the OAT gene family and characterization of the members of the family including the functional OAT gene, construction of expression clones of OAT and expression of OAT in heterologous tissues, and analysis of the OAT gene and its expression in GA patients which has revealed a case with a partial heterozygous deletion of the OAT gene and complete absence of the OAT mRNA. By examining the family members of this GA patient we were able to demonstrate the stable autosomal recessive inheritance of the OAT gene and expression defect in the family in addition to demonstrating the co-dominant mode of action of the OAT gene. Analysis of a GA patient who shows a marked decrease in the level of cellular OAT protein revealed that he is expressing only one of the two alleles of the OAT gene and that the expressed OAT contains a single point mutation resulting in an amino acid change. This amino acid change appears to modify an α-helical region of the OAT protein, and assay of the mutant OAT protein for mitochondrial transport/processing seems to indicate that the mutant protein fails to become processed.

Hereditary Retinoblastoma and X-linked Ocular Diseases: Work on hereditary retinoblastoma is continuing with isolation of malignant revertants of non-malignant hybrids between Y79 retinoblastoma and NIH3T3 cells and expression cloning of genes that may alter the phenotype of retinoblastoma. A linkage of the OAT-related X chromosome genes to Norrie Disease and X-linked retinitis pigmentosa has been established using restriction fragment length polymorphisms detected by the OAT probe.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00003-16 LMOD

PERIOD COVERED

October, 1987 to September, 1988

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

Pharmacology of Ocular Complications

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

PI:	Peter F. Kador	Ph.D.	Research Chemist	LMOD	NEI
Others:	Laure Caspers-Velu	M.D.	Visiting Scientist		
	Hitoshi Ikebe	M.D.	Visiting Scientist	LMOD	NEI
	Toshihiro Nakayama	Ph.D.	Visiting Scientist	LMOD	NEI
	Sanai Sato	M.D.	Visiting Scientist	LMOD	NEI
	Susan DiCamillo	B.A.	Guest Worker	LMOD	NEI

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Mechanisms of Ocular Disease

SECTION

Section of Molecular Pharmacology

INSTITUTE AND LOCATION

National Eye Institute, National Institutes of Health, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
6	5	1

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

The onset and progression of various ocular complications are being investigated as well as methods for their potential pharmacological control. Specifically, relationships between diabetes and galactosemia-induced retinopathy, cataract, keratopathy, and changes in pupil function, iris and ciliary process structure and the interactions of the enzymes aldose reductase and aldehyde reductase are being investigated. Methods for either delaying or preventing the onset and progression of these complications through the pharmacological control of these enzymes are also being developed.

Events leading to the formation of several types of cataracts are also being studied as well as methods for controlling the onset of these cataracts through pharmacological intervention.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00243-02 LMOD

PERIOD COVERED

October 1, 1987 to September 30, 1988

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

Ocular Cells Cultured Under Normal and Diabetic Conditions

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

PI:	Bruce A. Pfeffer	Ph.D.	Senior Staff Fellow	LMOD, NEI
Others:	W. Gerald Robison	Ph.D.	Chief, Section on Pathophysiology	LMOD, NEI

COOPERATING UNITS *(if any)*

None

LAB/BRANCH

Laboratory of Mechanisms of Ocular Diseases

SECTION

Section on Pathophysiology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, MD 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.0	2.0	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.)*

Along with the vascular lesions characteristic of diabetic retinopathy, considerable clinical evidence exists that the retinal pigment epithelium (RPE) is affected in diabetic eye disease. Biochemical and physiological studies of animal models suggest that diabetic pigment epitheliopathy may be a complication mediated by the activity of the enzyme aldose reductase. We are utilizing cultured human and monkey RPE as an in vitro model system to study the effects of elevated hexoses on these cells. In common with other tissues in the presence of high sugar concentrations, transport of the amino acid taurine into cultured RPE cells incubated with galactose is impaired. In addition, the galactose-treated cells are "leakier" in such a way as to actually extrude taurine. Both of these effects can be partially prevented by incubation with aldose reductase inhibitor (ARI) supplemental to the galactose. Since taurine is essential for normal retinal function, a deficit in RPE handling of taurine under diabetic conditions may contribute to retinal pathology.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00149-15 LMOD

PERIOD COVERED

October 1, 1987 to September 30, 1988

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 Pathophysiology	LMOD, NEI
Others:	Masao Nagata	Ph.D. M.D.	Visiting Associate	LMOD, NEI
	Bruce A. Pfeffer	Ph.D.	Senior Staff Fellow	LMOD, NEI

COOPERATING UNITS (if any)

None

LAB/BRANCH

Laboratory of Mechanisms of Ocular Diseases

SECTION

Section on Pathophysiology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
5.2	5.0	.2

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

Diabetic retinopathy is mainly a vascular disease which first manifests itself by several histopathological lesions related to the integrity of capillary walls, including basement membrane thickening, loss of mural cells, and endothelial cell proliferation. We now find that there is another diabetes-related alteration in capillary walls which results in fewer mural-to-endothelial cell contacts, and may cause endothelial cell proliferation. Normally, junctional regions which permit cell-membrane-to-cell-membrane contacts between mural and endothelial cells occur frequently. They appear as fenestrae in the thick basement membranes which separate the plasma membranes of the mural and endothelial cells over most of their juxtaposed surfaces. In galactose-fed rats there is a significant decrease in the number of junctional regions. After 28 months of normal diet there was a mean of 1.0 (range 1-6) junctional region per ultrathin transection of rat retinal capillaries, whereas, rats fed 50% galactose had less than half as many (mean = 0.3). When an aldose reductase inhibitor was added to the galactose diet the number of junctional regions approached normal (mean = 0.8). Therefore, as with several other diabetic complications, the decrease in cell-to-cell contacts in capillary walls is prevented by inhibition of aldose reductase activity. The mechanism of cell contact loss will be investigated using cell culture. Aldose reductase inhibitors are becoming increasingly useful in studies related to the possible prevention of diabetic retinopathy.

ANNUAL REPORT
NATIONAL EYE INSTITUTE
October 1, 1987 to September 30, 1988

REPORT OF THE CHIEF, LABORATORY OF MOLECULAR AND DEVELOPMENTAL BIOLOGY

Joram Piatigorsky, Ph.D.

This is the seventh year for the Laboratory of Molecular and Developmental Biology (LMDB). The efforts of this laboratory continue to be directed towards understanding the molecular and cellular basis for lens development. The complexion of the laboratory has changed this year, in that Dr. Toshimichi Shinohara has left to create a molecular biology section in the Laboratory of Immunology. We are fortunate, however, that Dr. Ana Chepelinsky has become a tenured member of the LMDB and has begun to form a productive research team. She is continuing her studies on the tissue-specific expression of the mouse αA-crystallin gene as she plans new investigations concerning the expression of non-crystallin genes in the lens. She has been a pivotal force in the creation of our transgenic mouse facility, presently housed in building 14. With Eric Wawrousek she has been able to demonstrate that the promoter for the mouse αA-crystallin gene retains its lens-specific activity in transgenic mice when a sequence containing only nucleotides -88 to +46 are used. This is of great interest, because in comparison with numerous other results we have obtained using chicken and mice it indicates that homologous crystallin genes do not use the same regulatory elements for their expression. Our ability to produce transgenic mice is continually being strenghtened and we now have trained two more investigators to do this demanding technique--Teresa Lomjoco and Joan McDermott.

As we continue to identify regulatory regions of the crystallin genes, we have increased our efforts to isolate the factors with which they interact. Two approaches are being developed in this connection. First, we are searching for lens nuclear proteins that bind to the crystallin gene regulatory regions. This requires the preparation and fractionation of proteins from lens cell nuclei. At the time of writing, David Donovan has resolved by ion-exchange chromatography chicken lens nuclear proteins which bind to the αA-crystallin promoters of chicken and mice. Working with Christina Sax and John Klement, Dr. Donovan has obtained preliminary evidence that these homologous crystallin promoters do indeed bind to different proteins, as the results above suggested. Moreover, it begins to look as if we might be able to purify these different putative regulatory proteins and their cDNAs. This would constitute a significant advance in our ability to understand how the complex temporal and spatial patterns of crystallin gene expression are regulated.

Binding alone is insufficient to reconstruct the dynamics of crystallin gene expression. It is necessary to develop functional assays for regulatory factors. Dr. Sax has explored the possibility of injecting crystallin promoters into Xenopus oocytes as a functional test for activity. Preliminary results indicate that this system may be used for identifying crystallin transcription factors. Ultimately we may have to devise a cell-free system as well which behaves with specificity with respect to crystallin transcription.

In addition to investigating the αA-crystallin gene in greater detail, we are also examining other crystallin genes. John Roth is in the process of mapping the different regulatory regions of the chicken βB1-crystallin gene and George Thomas is investigating the two chicken δ-crystallin genes. We have obtained evidence by using deletion mutants that these genes have upstream sequences repressing gene expression as well as more proximal positive regulatory regions. Chicken δ-crystallin is particularly intriguing in that there are two extremely similar genes lying side by side on the chromosome, yet one is expressed about a hundred times more strongly in the lens than the other. It appears as if a variety of regulatory mechanisms govern crystallin gene expression and the challenges before us are to understand how any one of these operates and how the different mechanisms are coordinated to achieve the perfection of a transparent lens.

Last year we reported that many crystallins, surprisingly, were recruited from metabolic enzymes. Graeme Wistow discovered that ε-crystallin is similar to lactate dehydrogenase B and even has enzyme activity. We went on to link τ-crystallin with enolase, δ-crystallin with argininosuccinate lyase and the squid crystallin with glutathione S-transferase. This year Dr. Wistow, Tom Lietman, Barbara Norman, and I have demonstrated that these crystallins are encoded by the same gene as their respective enzymes, a situation we call gene sharing. This has important implications for the evolution and expression of these crystallins. From an evolutionary viewpoiont, gene sharing means that a single protein is under at least two entirely separate selective pressures, which would slow the evolutionary clock. It also means that the different uses of this gene, i.e. as a structural crystallin protein in the lens or as an enzyme in other tissues, evolved by modification of gene regulation alone and did not involve changes in the coding regions of the genes. From an expression viewpoint, gene sharing means that crystallins are not lens-specific, but are only preferentially expressed in that tissue. When the crystallin/enzyme gene is being utilized as an enzyme it is expressed at low levels in many different tissues. We must still find out whether the same or different regulatory sequences are used for lens and non-lens expression of a shared gene and whether different transcription factors are invoked when the gene is used in one capacity or another. The surprising and fascinating finding that crystallins and metabolic enzymes share genes changes our thinking of the evolution and regulation of crystallins.

In contrast to the lens-specific expression of the αA-crystallin gene, studies by Robert Dubin have shown that the αB-crystallin gene is expressed in a number of different tissues, including heart, kidney and skeletal muscle. This suggests strongly that even crystallins with no known enzymatic function have another use in different tissues. Dr. Dubin showed by creating transgenic mice carrying an αB-crystallin minigene that lens and non-lens expression of this gene is regulated by its flanking sequences, most probably at the 5′ end. One wonders how many other proteins have multifunctional roles, and what were the rules to select such a smorgasbord of proteins to be used as lens crystallins.

In order to gain a fuller appreciation for the variety of proteins used as crystallins and to explore new terrain that may provide insight to the evolution of crystallin gene regulation, we are including invertebrates in our research. Last year we introduced the jellyfish as a subject of investigation since they have cellular lenses with a striking resemblance to vertebrate lenses, yet are extremely primitive animals (at least 600 million years old) which are, of course, built on an entirely different body plan than vertebrates. We have now shown that cubomedusan jellyfish lenses contain only 2 or 3 crystallins (depending upon species) which bear little if any similarity with the crystallins of the squid or vertebrates. We have generated an antibody to one of the jellyfish crystallins and are ready to isolate its cDNA and gene. We hope that these studies into the unchartered waters of invertebrate crystallins will yield surprises and valuable information concerning the evolution and expression of these gene families.

The work of Peggy Zelenka and her group concerns the expression of proto-oncogenes during differentiation of lens epithelial cells into lens fiber cells. Earlier studies from this section established that c-myc mRNA levels in cultured embryonic chicken lens epithelial explants were elevated as the cells withdrew from the cell cycle during differentiation. Using a modified nuclear run-on transcription assay which they developed, Dr. Zelenka has now demonstrated that the increased mRNA levels are at least partly regulated by increased transcription of exons 2 and 3 of the c-myc gene. Luke Pallansch has further demonstrated that c-myc mRNA levels in the cultured explants can be post-transcriptionally regulated by pharmacological agents which block the lipoxygenase pathway of arachidonic acid metabolism. In addition, Dr. Pallansch has shown that a lipoxygenase pathway metabolite of arachidonic acid is lost during in vitro differentiation, raising the possibility that this post-transcriptional mechanism may also be involved in the accumulation of c-myc mRNA that accompanies differentiation.

Efforts to measure levels of c-myc protein in the past had been fruitless because of the failure of chicken c-myc protein to cross-react immunologically with available antisera against the human and mouse proteins. This year Howard Beswick and John Talian planned and oversaw the synthesis and purification of chicken-specific c-myc peptides, which were then used to raise antibodies in rabbits. As a result it is now possible to establish the relationship between c-myc protein and mRNA levels in differentiating lens cells. This antiserum also makes possible a variety of experiments on the distribution, stability, and function of c-myc protein during differentiation.

Since expression of high levels of c-myc protein is not correlated with DNA replication in differentiating lens cells, other possible functions for this protein are being considered. Dr. Zelenka, working with Anita Dash, a summer student, has demonstrated that elevated c-myc expression is correlated with accumulation of mRNA for the heat shock protein, HSP 70. In addition, Dr. Howard Beswick has constructed a plasmid containing a chicken c-myc cDNA which will allow experiments to study the effect of c-myc expression on the transcription of other genes in transfected cells.

Dr. Talian has begun an investigation of the expression of a cytoplasmic proto-oncogene, c-src, in embryonic chicken lenses. As a preliminary step, he has studied the expression and distribution of calpactin I, a protein which is a known substrate for the tyrosine kinase activity of v-src, and which has recently been shown to be a major component of the lens membrane EDTA-extractable protein fraction by a collaborative effort between this laboratory and Dr. Paul Russell (NEI,LMOD). Using immunofluorescence, Dr. Talian has established that calpactin I has the expected localization along membranes of lens fiber cells, and has shown for the first time that this protein is present in lens epithelial cells. Using cultured explants of embryonic chicken lens epithelia he has shown that the intensity of immunofluorescence for calpactin I increases during the first 24 hr of differentiation in vitro, in parallel with accumulation of calpactin I mRNA. These studies point to increased synthesis and accumulation of calpactin I during early stages of lens fiber formation, and are consistent with the suggestion that this protein may play a role in the cell elongation that accompanies differentiation.

It is too often taken for granted that a laboratory runs smoothly without the realization that this only occurs when its support staff is excellent. Our secretary, Mrs. Dawn Chicchirichi, continues to take care of all our administrative and typing needs and we are very lucky to have her with us. We also rely heavily on Mrs. Barbara Norman who keeps the laboratory well-oiled and in top shape as she performs her "bench work". I take this opportunity to thank them and make my appreciation known.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00127-12 LMDB

PERIOD COVERED

October 1, 1987 to September 30, 1988

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
	John Talian	Ph.D.	IRTA Fellow	LMDB, NEI

COOPERATING UNITS *(if any)*

Flora de Pablo	M.D.	Diabetes Branch, NIDDK

LAB/BRANCH

Laboratory of Molecular and Developmental Biology

SECTION

Section on Cellular Differentiation

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.5	2.5	0

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

This project has identified a wide range of alterations in plasma membrane lipids and proteins which are associated with differentiation of lens epithelial cells to form lens fibers. Results have shown that phosphatidylinositol degradation ceases when lens epithelial cells differentiate to form lens fiber cells, while synthesis of phosphatidylinositol and other phospholipids increases. Since phosphatidylinositol is rich in arachidonic acid, a precursor of prostaglandins and leukotrienes, the metabolites of arachidonic acid produced by lens cells have been characterized. Loss of a lipoxygenase pathway metabolite has been correlated with the initiation of differentiation in vitro. Plasma membrane proteins which have been investigated include the insulin and IGF receptors and the membrane associated protein, calpactin I. Equilibrium binding studies have shown that embryonic chick lens epithelial cells possess both insulin and IGF I receptors, and that expression of both is regulated during differentiation and development. Analysis of membrane associated proteins has demonstrated that calpactin I is a major component of the EDTA-extractable protein of lens membranes. mRNA for this protein accumulates during in vitro differentiation, in parallel with an increase in immunofluorescence staining intensity. These studies have shown that embryonic chicken lens epithelial membranes are dynamic entities which undergo structural and functional changes as part of the differentiation process.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00238-03 LMDB

PERIOD COVERED

October 1, 1987 to September 30, 1988

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

Proto-oncogene Expression During Lens Differentiation and Development

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
	Howard Beswick	Ph.D.	Visiting Fellow	LMDB, NEI
	Xiu-An Zhu	M.D.	Visiting Scientist	LMDB, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Molecular and Developmental Biology

SECTION

Section on Cellular Differentiation

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

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

This project investigates the expression of proto-oncogenes during the differentiation of embryonic lens epithelial cells to form lens fiber cells, and seeks to determine the specific function of the corresponding gene products in the developing lens. Measurements of steady-state mRNA levels and nuclear run-on transcription experiments have identified several proto-oncogenes which are actively expressed in the embryonic lens. Among these are the nuclear proto-oncogenes, c-myc, c-fos, and p53, and the membrane-associated tyrosine-specific protein kinase, c-src. A transient increase in the expression of the c-myc gene which occurs as the differentiating cells withdraw from the cell cycle suggests that this proto-oncogene may regulate some aspect of differentiation. The increased expression of c-myc has been shown to be primarily post-transcriptional, although a small increase in transcription has also been observed. The increase in c-myc expression which occurs during differentiation can be mimicked pharmacologically by agents which block the lipoxygenase pathway of arachidonic acid metabolism. Increased levels of c-myc mRNA, whether in differentiating cells or in cells treated with lipoxygenase inhibitors, are correlated with accumulation of mRNA for the heat shock protein, HSP70.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00126-07 LMDB

PERIOD COVERED

October 1, 1987 to September 30, 1988

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

Crystallin Genes: Structure, Organization, 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:	Ana B. Chepelinsky	Ph.D.	Research Biologist	LMDB, NEI
	David M. Donovan	Ph.D.	IRTA Fellow	LMDB, NEI
	Robert A. Dubin	Ph.D.	Staff Fellow	LMDB, NEI
	John F. Klement	Ph.D.	Staff Fellow	LMDB, NEI
	Thomas Leitman	B.A.	HH Medical Student	LMDB, NEI

COOPERATING UNITS *(if any)*

See next page

LAB/BRANCH

Laboratory of Molecular and Developmental Biology

SECTION

Section on Molecular Genetics

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
12	12	0

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

We have continued to study the crystallin genes and their expression in the cellular eye lens. Experiments have provided evidence that the chicken and mouse αA-crystallin gene use different cis-acting sequences and trans-acting factors to regulate their expression. Partial purification of embryonic chicken lens nuclear proteins that bind to the mouse αA-crystallin promoter has been achieved. More importantly, it appears as if it will be possible to isolate these putative regulatory proteins and their cDNAs. In contrast to the αA-crystallin gene, which is highly lens-specific, the mouse αB-crystallin genes were shown to be expressed in numerous non-lens tissues (heart, kidney, skeletal muscle), although to a lesser extent than in lens. Experiments using cultured cells and transgenic mice indicated that regulation of the αB gene resides in its 5′ flanking sequence. The chicken βB1-crystallin promoter has been shown to be lens-specific in cultured cells; deletion mutants suggested the presence of a negative regulatory sequence (-436/-296) in this gene which may contribute to its tissue-specific expression. The concept of gene sharing was developed, which refers to the same gene encoding both a lens crystallin and a metabolic enzyme. Our data indicate that argininosuccinate lyase is encoded by the δ-crystallin genes (possibly only the δ2 gene in the chicken) and α-enolase by the single τ-crystallin gene in ducks and chickens. The τ-crystallin/α-enolase gene in ducks is expressed about 25 times more strongly in the lens than in the liver. Finally, sequences of tryptic peptides were obtained and an anti-serum was raised to a synthetic peptide specific for a major crystallin (J1) of the jellyfish eye lens. This initiates molecular studies on the crystallin of these ancient cellular lenses.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 EY 00251-01 LMDB

PERIOD COVERED

October 1, 1987 to September 30, 1988

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

Regulatory elements of the αA-crystallin gene promoter

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

PI:	Ana B. Chepelinsky	Ph.D.	Research Biologist	LMDB, NEI
Others:	Teresa Limjoco	M.D.	Visiting Fellow	LMDB, NEI
	Eric Wawrousek	Ph.D.	Staff Fellow	LMDB, NEI
	Joram Piatigorsky	Ph.D.	Chief	LMDB, NEI
	Bernd Sommer	Ph.D.	Guest Worker	LMDB, NEI

COOPERATING UNITS *(if any)*

Clive Dickson	Ph.D.	Imperial Cancer Research Fund London, England

LAB/BRANCH

Laboratory of Molecular and Developmental Biology

SECTION

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3	3	0

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

We have continued to characterize the cis-regulatory elements of the murine αA-crystallin promoter responsible for the lens-specific expression of this gene. Hybrid genes containing murine αA 5′ flanking sequences and the gene coding for the bacterial enzyme chloramphenicol acetyltransferase (CAT) were constructed and their expression studied in explanted chicken lens epithelia and in transgenic mice. Our results indicated the presence of a proximal (-88/+46) and a distal (-111/-88) domain which must interact for promoter function in the explanted chicken lens epithelia. The sequence -88/-60 is essential for promoter function. The distal domain activates the proximal domain when placed at the 5′ end but not when inserted at the 3′ end of the CAT gene. The distal domain does not activate the enhancerless SV40 promoter. Point mutations indicated that bases at positions -108 and -109 are essential for the activating properties of the distal domain in explanted chicken lens epithelia. Experiments with transgenic mice showed that the sequence -88/+46 directs CAT gene expression specifically to the lens. Gel retardation and methylation interference experiments provided evidence for selective binding of different embryonic chicken lens nuclear proteins to sequences -111/-84 and -83/-55. The protein factor binding -111/-84 may have some similarities to the transcription factor Sp1.

ANNUAL REPORT
NATIONAL EYE INSTITUTE
October 1, 1987 - September 30, 1988

REPORT OF THE CHIEF, LABORATORY OF RETINAL CELL AND MOLECULAR BIOLOGY

Gerald J. Chader, Ph.D.

The mission of the Laboratory of Retinal Cell and Molecular Biology is to investigate the functioning of the neural retina, at the levels of both cell and gene functioning. To best achieve this goal, investigators in the Laboratory are grouped in three Sections, although there is a great deal of communication and collaboration between the groups.

Following are some of the accomplishments of the Laboratory members in this past year:

Section on Cell Biology: A possible defect in phospholipid metabolism has been uncovered in a canine model of inherited retinal degeneration. Palmitic acid incorporation is abnormal in affected dogs, suggesting a significant reduction in the esterification of palmitic acid in this disease. Another important finding is that the alkylating agent NMNN can induce a progressive retinal degeneration in test animals. This effect appears at the gene level. Thus, two important leads have been uncovered in approaching genetic and toxicologically-induced degenerative conditions of the neural retina.

Section on Biochemistry: Members of this Section have also studied animal models of retinal degeneration. In this case, the hereditary models used were in mouse, cat and dog. Interestingly, an early defect in the secretion of the photoreceptor protein IRBP, interphotoreceptor-binding protein, was found. The rd gene in particular appears to code for this secretion defect. A related project of investigators in this Section is the study of animal models of human uveitis. With collaborators in the Laboratory of Immunology, the IRBP protein has been found to be highly uveitogenic, inducing a severe inflammatory condition in the eyes of mouse, rat and monkey. Moreover, small peptide fragments of the IRBP molecule have been pinpointed that cause the disease. This is a potentially major breakthrough that may allow for modes of therapy to be developed in the future.

Section on Gene Regulation: This group has been very successful in investigating the IRBP gene. The entire bovine genomic IRBP has been cloned and fully sequenced. The protein is large, the mRNA is also large but the gene is relatively compact. The full amino acid sequence has been deduced from the nucleotide sequence; it has given clues as to many of the interesting functional domains in the IRBP molecule. For example, it can be seen that the protein is composed of four similar units, two of which may cooperate to bind a retinoid molecule. The four-fold repeat strongly indicates gene replication during evolution. These findings will make it possible to begin the study of gene expression of IRBP in test systems in the near future.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 EY 00070-11 LRCMB

PERIOD COVERED

October 1, 1987 to September 30, 1988

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.	Head, Section on Biochemistry	LRCMB, NEI
Others:	Ling Lee	M.S.	Chemist	LRCMB, NEI
	Michael Redmond	Ph.D.	Staff Fellow	LRCMB, NEI
	Gerald J. Chader	Ph.D.	Chief	LRCMB, NEI

COOPERATING UNITS *(if any)*

LSU Eye Center, New Orleans, LA (N. Bazan, B. Scott); Johns Hopkins University, Baltimore, MD (R. Adler); University of Lund, Lund, Sweden (T. van Veen); University of Illinois College of Medicine, Chicago, IL (D. Pepperberg, H. Ripps)

LAB/BRANCH

Laboratory of Retinal Cell and Molecular Biology

SECTION

Section on Biochemistry

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.7	1.7	1.0

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

Interphotoreceptor retinoid binding protein (IRBP) was studied in retinae of mice with allelic combinations at the rd and rds loci. Until postnatal day 7 (P7), IRBP is located intracellularly in all retinae. Thereafter, in the normal retina, IRBP increases and is found primarily in the interphotoreceptor matrix. In the rd/rd, +/+, and rd/rd, rds/rds mutants, IRBP drops rapidly after P11 and is not secreted but is present intracellularly during the remaining degenerative process. In the rd/rd, rds/rds mutant, IRBP loss significantly precedes visual cell loss. In contrast, retinae of rodless +/+, rds/rds and +/+, rds/+ mutants synthesize essentially normal amounts of IRBP until very late in the degenerative process when there is then a significant amount of intracellular IRBP. We conclude that abnormality in secretion combined with other factors could lead to the degenerated phenotype in mice bearing the rd gene.

Four synthetic peptides based on amino acid sequences present in cyanogen bromide peptides of IRBP were shown to induce autoimmune uveitis (EAU) and pinealitis (EAP) in Lewis rats. One of these peptides, containing 23 amino acids, was highly immunopathogenic and also immunodominant. The other peptides were substantially less immunopathogenic and also non-dominant.

IRBP was found to provide efficient delivery of retinol to the pigment epithelium for esterification and storage in the eyecup of dark adapted toads (B. Marinus). Purified bovine IRBP was found to be capable of binding exogenous radiolabeled docosahexaenoic acid and palmitic acid.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00015-23 LRCMB

PERIOD COVERED

October 1, 1987 to September 30, 1988

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	Ph.D.	Head, Section on Cell Biology	LRCMB, NEI
Others:	Sylvia B. Smith	Ph.D.	IRTA Fellow	LRCMB, NEI
	Caren C. Demars	B.A.	Biologist	LRCMB, NEI

COOPERATING UNITS (if any)

LAB/BRANCH

Laboratory of Retinal Cell and Molecular Biology

SECTION

Section on Cell Biology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

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

CHECK APPROPRIATE BOX(ES):

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

☐ (a1) Minors

☐ (a2) Interviews

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

The post-translational modifications of rhodopsin include acylation, glycosylation and chromophore addition. All appear to take place in the rod inner segment. The resulting molecules exhibit a slightly higher molecular weight than the mature rhodopsin in the outer segment and thus can be distinguished. The role of the palmitate residues is unknown but could be related to membrane assembly. The addition of the vitamin A chromophore seems to be essential for intracellular transport of the opsin protein to the Golgi and to the outer segments. The addition of several sugar residues in the Golgi complex may be a requirement for normal outer segment disc formation since the rhodopsin molecules in the plasma membrane and basal folds have a higher molecular weight than rhodopsin in disc membranes.

Rod outer segments contain a molecule with both inositol and glucosamine. This molecule is reminiscent of the phosphatidylinositol-glycan anchor found in transiently membrane bound proteins and may indicate the existence of a phospholipase mediated release mechanism.

A manganese-dependent 5'-nucleotidase that cleaves cytidine monophosphate has been found to become highly active in rod outer segment tips at the time of disc shedding. It has been isolated, partially purified and characterized and could provide insight into new mechanisms related to the shedding process.

PROJECT NUMBER

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 EY 00016-21 LRCMB

PERIOD COVERED

October 1, 1987 to September 30, 1988

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	Ph.D.	Head, Section on Cell Biology	LRCMB, NEI
Others:	Sylvia B. Smith	Ph.D.	IRTA Fellow	LRCMB, NEI
	Caren C. Demars	B.A.	Biologist	LRCMB, NEI

COOPERATING UNITS (if any)

School of Veterinary Medicine, University of Pennsylvania (G. Aguirre)

LAB/BRANCH

Laboratory of Retinal Cell and Molecular Biology

SECTION

Section on Cell Biology

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.1	0.9	0.3

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

This project examines biochemical events unique to the retina, particularly the synthesis and modification of photoreceptor membrane components, in the retinas of vertebrates which can be affected by inherited retinal degenerations. The synthesis of the visual pigment, rhodopsin, occurs at a normal rate as measured by radioactive leucine incorporation following intravitreal injection in the eyes of miniature poodles affected with progressive rod-cone degeneration. Similarly, the glycosylation and acylation of rhodopsin were found to be normal following intravitreal injection of labeled fucose or palmitic acid, respectively. However, phospholipid synthesis or degradation, measured by radioactive palmitic acid incorporation, appears to be different in the affected dogs, suggesting a possible metabolic defect in this inherited disorder. The evidence suggests a significant diminution in the esterification of palmitic acid. Incubation of trephine punches of retina with labeled precursors produces the same labeling pattern in phospholipids as does intravitreal injection. Thus many precursors can be screened with a single retina.

Transplacental exposure to the DNA alkylating reagent N-methyl-N-nitrosourea on day 16 of gestation in CD-1 albino mice induces a progressive retinal degeneration beginning at 4-6 weeks of age. No obvious defect in either protein or phospholipid synthesis can be demonstrated. Thus a more subtle defect may have occurred such as the alteration of a small number of genes.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00148-15 LRCMB

PERIOD COVERED

October 1, 1987 to September 30, 1988

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

Visual Control Mechanisms

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

PI:	Gerald J. Chader	Ph.D.	Chief	LRCMB, NEI
Others:	R. Theodore Fletcher	M.S.	Chemist	LRCMB, NEI

COOPERATING UNITS *(if any)*

School of Veterinary Medicine, University of Pennsylvania (G. Aguirre); Department of Anatomy, Erasmus University, Rotterdam, The Netherlands (S. Sanyal); Department of Zoology, University of Lund, Lund Sweden (T. van Veen)

LAB/BRANCH

Laboratory of Retinal Cell and Molecular Biology

SECTION

Section on Gene Regulation

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
0.7	0.2	0.5

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

Several diseases appear to only strike the neural retina. Thus, there may be important proteins or other substances that are specific to the retina and which are abnormal either in function or concentration in these retinal diseases. Such a protein may be IRBP, the interphotoreceptor retinoid-binding protein. We have found a greatly decreased concentration of this protein in an early stage of hereditary retinal degeneration in the Abyssinian cat. Other proteins may not be retina-specific but possible defects in their synthesis and/or function may particularly affect retinal metabolism. Such a protein, the cAMP-dependent protein kinase, is found in many cell types but appears to have a defect in synthesis in retinoblastoma tumor cells grown in tissue culture. Such a defect could cause or contribute to the uncontrolled growth of retinoblastoma cells in vitro and perhaps in vivo as well.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00124-08 LRCMB

PERIOD COVERED

October 1, 1987 to September 30, 1988

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 personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	Gerald J. Chader	Ph.D.	Chief	LRCMB, NEI
Others:	Robert Waldbillig	Ph.D.	Expert	LRCMB, NEI
	R. Theodore Fletcher	M.S.	Chemist	LRCMB, NEI
	Dagmar Arnold	M.D.	Visiting Associate	LRCMB, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Retinal Cell and Molecular Biology

SECTION

Section on Gene Regulation

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.3	1.8	0.5

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

Low molecular weight, soluble factors as well as extracellular matrix molecules play major roles in the growth and development of all tissues. This includes normal tissue and tumor tissue. Laminin may play such a critical role in retinal development. Insulin and especially IGF-1 may act as messengers coding for differentiation in the retina and, by affecting phosphorylation of the G-protein transducin, may be directly or indirectly involved in the visual process. Abnormal protein kinase activity and thus cyclic AMP function may be involved in the rapid, uncontrolled growth of retinoblastoma tumor cells.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

PROJECT NUMBER

NOTICE OF INTRAMURAL RESEARCH PROJECT

Z01 EY 00196-05 LRCMB

PERIOD COVERED

October 1, 1987 to September 30, 1988

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 personnel below the Principal Investigator.) (Name, title, laboratory, and institute affiliation)*

PI:	John M. Nickerson	Ph.D.	Biologist	LRCMB, NEI
Others:	Diane Borst	Ph.D.	IRTA Fellow	LRCMB, NEI
	T. Michael Redmond	Ph.D.	Staff Fellow	LRCMB, NEI
	Jing-Sheng Si	M.D.	Visiting Associate	LRCMB, NEI
	Adriana Albini	Ph.D.	Visiting Associate	LRCMB, NEI
	Lila Inouye	M.D.	Staff Fellow	LRCMB, NEI
	Judith Toffenetti	Ph.D.	Staff Fellow	LRCMB, NEI

COOPERATING UNITS *(if any)*

See next page.

LAB/BRANCH

Laboratory of Retinal Cell and Molecular Biology

SECTION

Section on Gene Regulation

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
6.2	6.2	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.)*

My laboratory has isolated and characterized recombinant DNA molecules necessary for the study of the structure and expression of IRBP (Interphotoreceptor Retinoid-Binding Protein). We have cloned many different cDNAs (copies of the IRBP messenger RNA) from bovine and human retina. We have screened a human retina cDNA library with the bovine IRBP cDNA probe and have identified several large cDNA clones up to 3.5 kb in length for human IRBP. We have sequenced portions of all of these overlapping cDNA clones. The IRBP mRNA is long, 4.4 to 7.4 kb in several species and usually gives only one band on a Northern blot. The cDNA and gene sequences have been used to predict the amino acid sequence of the protein. The polypeptide contains four 300 amino acid long repeats, with 30-40% identity among the repeats. These sequences have been helpful in the analysis of the uveitogenic peptides in IRBP. DNA sequence analysis of the gene clone has identified the authentic N-terminus, the putative initiator methionine codon, a putative pro-peptide and a putative signal peptide sequence of the IRBP polypeptide. The chromosomal location of the IRBP gene is: 10 for human, 4 for dog, and 11 for mouse. The bovine gene structure is compact for the size of the protein, and has only 3 introns. The structure of the gene suggests an interesting evolution, involving a processed gene intermediate and two unequal crossovers.

ANNUAL REPORT
NATIONAL EYE INSTITUTE
October 1, 1987 - September 30, 1988

REPORT OF THE CHIEF, LABORATORY OF SENSORIMOTOR RESEARCH
Robert H. Wurtz, Ph.D.

This is the Tenth Annual Report of the Laboratory of Sensorimotor Research. Rather than summarize last year's work (which is detailed in the following individual annual reports) I would like to outline the progress of the Laboratory in its first decade. Even this unusually long report describes only major themes, omitting a series of other important areas of work within the laboratory.

The investigators in this Laboratory share an interest in the brain mechanisms underlying vision and eye movement. Three fields of neurophysiology that are particularly well developed relate to the control of eye movements: the processing of visual target information, the generation of eye muscle innervation, and the adaptive maintenance of adequate performance. Knowledge in these fields has advanced rapidly over the last twenty years, and members of the Laboratory have been at the forefront of each field. Despite this progress, one of the great unresolved problems in neurophysiology remains: how does sensory information give rise to motor responses? One of the goals of the Laboratory has been to study not only the individual aspects of visual and motor processing by the brain, but also the transition from visual to motor signals.

The visual and oculomotor functions of the brain that we study have been shown to be similar in humans and old world monkeys (Macaca mulatta) so that our experiments on the monkey serve as a model for humans. Behavioral, physiological, and anatomical experiments that are possible in the monkey have given us our most fundamental understanding of how visual and oculomotor functions are likely to be organized in humans. In addition, several investigations in the laboratory illustrate how the precise analysis possible in the visual-oculomotor system has allowed exploration of more general questions of brain research.

One of the major advantages of studying this visual-oculomotor system is that this system consists of a series of simple movement subsystems, all integrated to produce a coordinated system, but each sufficiently separated to allow each to be studied individually. Work in the laboratory has concentrated on a number of these movement systems including the saccadic, pursuit, and ocular following systems.

Saccadic eye movements. These movements shift the direction of the eye rapidly from one part of the visual field to another to bring the fine-grained fovea of the retina onto the area of the visual field of interest. This is the system whose integrity is critical for reading and for the frequent inspection of our surroundings.

Dr. Michael Goldberg has concentrated on an understanding of the saccadic system at the highest level of organization, the frontal region of the cerebral cortex. In an area that is referred to as the frontal eye fields, he has

identified a set of neurons that are active during different phases of the saccadic eye movement including cells responding to visual stimuli, cells discharging in association with purposive eye movements, and cells discharging after the occurrence of an eye movement. He has found that the cells discharging in relationship to eye movements represent the major output of this cortical area to the brainstem structure related to saccadic eye movements, the superior colliculus. Removal of these cortical cells by selective lesion has revealed that a significant function of the area is the generation of saccadic eye movements under complex conditions, e.g., saccades made to the location of a remembered target.

Work on the frontal eye fields has dealt with one of the most fundamental problems that the brain must solve in controlling movement: the conversion of a sensory error into an accurate motor movement. For saccadic eye movements, this question is one of how the brain converts the difference between where the eye is looking and where the desired target is located into the spatial coordinates used to guide the eye movement. Most solutions to this problem hypothesize a spatial map within the brain, but only rudimentary spatial maps have been found. On the basis of his experiments, Dr. Goldberg developed an alternate hypothesis that argued that the brain uses only the difference in eye and target position but updates this difference information after every eye movement. All the elements necessary for this system have been identified in the activity of single cells in the frontal cortex. Thus, the work on the frontal eye fields has produced important hypotheses about the way the brain solves fundamental sensory motor problems and represents the most quantitative and detailed study of one of the highest levels of cortical function. Insights gained from this work have recently led to a method of treatment of patients whose reading is interrupted by extraneous saccades.

An area of the basal ganglia in the brainstem (the substantia nigra pars reticulata) receives projections from frontal cortex, and Dr. Hikosaka and I discovered that cells in this area that decrease their discharge in relation to saccades to visual targets or with saccades to locations that had to be remembered. Since the output of this structure has been demonstrated to be inhibitory on the next stage of the saccadic system, the superior colliculus, it is likely to exert a control on the superior colliculus not previously realized. We subsequently demonstrated such control by blocking or mimicking the action of the inhibitory transmitter, GABA in the pathway to the superior colliculus. Because of the precision of recording of saccadic eye movements and the control of the conditions under which they are made, this oculomotor-related pathway is probably the best understood output of the basal ganglia. Subsequent tests in humans with a disease of the basal ganglia (Parkinsons Disease) revealed some of the same deficits seen in the monkey during the treatment with drugs that mimic GABA.

A target of both the frontal eye fields and the substantia nigra is the superior colliculus and its relation to saccadic eye movements was first described by Goldberg and me nearly 20 years ago. Subsequent work in our laboratory and many others has contributed to defining the role of cells in the superior colliculus to the control of saccadic eye movements and the consequences of damage of the structure. The classic understanding of the colliculus has been that it has provided information on the motor error, the difference between position of the eye and the target. Work in the laboratory in the last several years has shown, however, that there are additional cells in the superior colliculus that provide information about how far the eye has gone toward reaching that target, a dynamic motor error.

One test of the completeness of the knowledge in a field is the ability to make mathematical models that perform realistically. Using knowledge common to the field, and the results of recent experiments within the Laboratory, Dr. Lance Optican has been able to develop a new model that incorporates both visual and motor elements of the saccadic system. This model incorporates physiological observations and produces dynamically realistic eye movements when simulated on a computer. Dr. Optican's model is a unique achievement in its successful description of how visual information may control saccades. The advantage of this modeling approach is that it suggests a new concept of the organization of the brain stem control of saccades, incorporates both new and old physiological observations, and reconciles seeming discrepancies among different experimental results. The model emphasizes the importance of some of our new observations on the superior colliculus, and has redirected study of the role of the superior colliculus in controlling eye movements throughout the field.

Our knowledge of the saccadic system is sufficiently extensive that it has warranted a volume in Reviews of Oculomotor Research, edited by me and Dr. Goldberg.

Pursuit eye movements. These movements allow the fovea to be directed at a target moving in the visual field, and among mammals this system is most highly developed in primates, including humans. An understanding of this system is dependent on an understanding of visual motion processing within the brain, which in primates is largely concentrated within the cerebral cortex. Work by me and my collaborators has capitalized on the identification of different cortical areas in front of the primary visual area, particularly areas MT and MST, where a high proportion of cells are sensitive to visual motion. We found that punctate chemical lesions of MT led to a deficit in pursuit but not saccades; this represents the clearest demonstration to date that an area of visual cortex can be related to one type of visual processing (motion) but not for another (position). Cells in MST provide both visual motion information and added non-visual information on direction of pursuit eye movements. Discrete damage to this area produces a deficit in pursuit toward the side of the brain with the lesion, as has been classically observed following damage to parietal cortex in humans.

Ocular Following Movements. Several types of eye movements have long been recognized to reduce slippage of the retinal image in order to provide clear and stable vision in spite of movements of the head and body: the vestibular-ocular response and the optokinetic response. Dr. Frederick Miles has now identified an entirely new visual-motor response not previously recognized that also aids in maintaining clear vision, and he has referred to this as an ocular following response. He has found in the monkey that this response has an incredibly short and regular latency close to 50 msec., and that it is generated by motion of the visual field. The sensitivity of the system is increased shortly after a saccade, and could serve to minimize in our normal complex environment the drifts of eye movement that follow saccades. Subsequent experiments have revealed a similar though not as robust ocular following response in humans. Through a series of ingenious experiments on the monkey, Dr. Miles and his collaborators have been able to dissect out the variables affecting this response and have suggested that the ocular following response is designed for stabilization of the visual scene during translation through the environment. This is in contrast to the optokinetic and vestibulo-ocular systems which stabilize the visual scene during rotation of the head and body. The recognition of this control system raises the possibility that a number of characteristics ascribed to other ocular motor

systems, such as the pursuit system, are actually part of this newly recognized translational control system. Dr. Miles' experiments also illustrate further the power of a carefully detailed behavioral analysis applied to a complex system within the brain.

Visual Selection. The selection of a target from among the myriad of those available is important for several forms of behavior and critical for the execution of saccadic eye movements. Dr. David Lee Robinson has concentrated on the neural basis of this selection process and more generally on visual attention independent of the direction of gaze. His work has concentrated on the pulvinar nucleus, a visual area in the thalamus, and much of our knowledge of the function of this structure is the result of his investigations. In studies of the pulvinar, superior colliculus, and parietal cortex, he has shown the modified responses of single cells while the monkey shifted attention from one part of the visual field to another, and has also been able to use small reversible chemical lesions to reveal the contribution of these structures to shifts of attention. These experiments not only demonstrate the ability to relate a brain structure to such a high level function as selective attention, but also show for the first time a function for the pulvinar, a hitherto puzzling thalamic structure. These insights into attentive processes have led to investigations of patients with diseases affecting the parietal and frontal regions of the cerebral cortex and progressive supranuclear palsy; such experiments reveal that different types of deficits are associated with damage to different regions of the brain.

Adaptive Control. The oculomotor systems, in order to function properly, must be continually adjusted for changes that occur normally in the course of developing and aging or that result from diseases affecting the system. Adjustment of these oculomotor systems therefore require adaptive control to maintain their precision, particularly if the system usually operates "open loop", that is, information about any error in the movement arrives in the brain too late to alter that movement. Dr. Miles and Dr. Optican have been leaders in investigating adaptive control in the oculomotor system. Before joining the laboratory, Dr. Miles had studied extensively the cellular changes related to the adaptive changes of the vestibular ocular reflex as well as the conditions under which this adaptation occurred, and since joining the laboratory he has shown that the plasticity of this system is so specific that adaptation can occur for certain frequencies of vestibular stimulation but not others. He and Dr. Optican showed that the amplitude of saccades and the subsequent ocular drifts were also subject to adaptive control. Subsequent work by Dr. Miles has revealed for the first time the adaptive control of vergence accommodation, and of the newly identified ocular following response. Dr. Optican was the first to demonstrate the adaptive control of the pursuit system. This was an important finding, since the pursuit system is not "open loop", i.e., pursuit movements are slow enough that they influence their input (retinal slip) and can provide adequate control. In this case, the adaptive control was designed to proved not merely adequate, but optimal, performance, and this finding raises the possibility that all neural systems are under adaptive control. The role of the cerebellum has been demonstrated in several of these cases of adaptation, giving this structure a major role in the adaptive control of eye movements, and probably a more explicit function than that postulated for any other system.

Visual Coding. While work in the laboratory has centered on visual-motor control, a number of experiments have concentrated on visual processing, particularly in the visual pathways from primary visual cortex into extrastriate areas

related to visual motion (MT and MST) and to areas presumably related more to the analysis of form (inferotemporal cortex). Salient among these investigations has been the work by Dr. Optican in collaboration with Dr. Richmond of the NIMH which questions the fundamental assumption of nearly all studies of the visual system that single neurons convey information only by the strength of their discharges. In their investigations on inferotemporal and striate cortex neurons, they have been able to show that the pattern of discharge is critical, and that the temporal modulation of the cell discharge contains roughly double the information transmitted by a neuron as compared to the total number of spikes alone. Drs. Optican and Richmond have developed hypotheses about how the visual system might encode within one neuron a series of visual characteristics of a stimulus. Their hypotheses raise fundamental questions about the way in which the brain codes visual information and additional fundamental questions about the organization of the visual system based on the notions of the tuning characteristics of individual neurons that has grown out of the work of Hubel and Wiesel in the last 25 years. Investigation of their hypothesis will yield fundamental insights on some of the most intriguing questions related to the visual system, namely, how such properties as form, color, and motion are represented by neurons within the brain.

The future challenge. In comparison to the challenge of understanding these elegant and precise visual and visual-motor systems within the brain, our progress has been modest. But in comparison to the knowledge that we had about these systems 10 years ago, I find our progress very gratifying. Because of the relative simplicity of the oculomotor system we probably now understand its subsystems better than any other other system in the primate, and the field of oculomotor control is the first within neurophysiology to be on the brink of understanding the entire flow of information from the visual sensation to the motor response. We look on the visual-motor function of the brain as providing clues to higher brain function. The number of fundamental problems already studied that relate to general issues of brain function indicate, I think, that this approach is successful. One of the most exciting challenges facing the Laboratory in the future will be to use our expertise in the study of visual, motor and adaptive neural mechanisms to produce a new field of sensorimotor physiology, one able to study the brain's systems as an integrated whole.

Our laboratory has benefited greatly from the interactions of a group of senior scientists working on different but related problems, and we have been able to share intellectual challenges and technical break throughs quickly and efficiently. It is obvious that there is extensive overlap in our interests that has led to substantial cross fertilization in both directions of experiments and experimental design. At a technical level we have benefited from technical advances now used beyond our laboratory: the implantation of the eye coil (Judge, Richmond and Chu), the Rex laboratory computer software, (Hays, Richmond and Optican), and the ASP model simulation software (Optican and Goldstein). In the 10 years since its organization, I think our laboratory has become preeminent in the study of the visual-motor system and, as a consequence, we are able to attract some of the most talented young investigators from throughout the world. I can only hope that the next 10 years will be as profitable as the last.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00049-10 LSR

PERIOD COVERED

October 1, 1987, to September 30, 1988

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 A. Segraves	Ph.D.	Senior Staff Fellow	LSR, NEI
	Edmond J. FitzGibbon	M.D.	Senior Staff Fellow	LSR, NEI
	Carol L. Colby	Ph.D	Guest Researcher	LSR, NEI
	Jean-Rene Duhamel	Ph.D.	Visiting Scientist	LSR, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Sensorimotor Research

SECTION

Neuro-Ophthalmologic Mechanisms Section

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
3.6	2.5	1.1

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

SUMMARY OF WORK *(Use standard unreduced type. Do not exceed the spece providad.)*

The functional nature of the projection from the frontal eye field to the brain stem has been studied in the rhesus monkey. Like the frontotectal projection, the frontopontine projection contains cells which discharge in association with eye movements or visual fixation, but not cells which have exclusive peripheral visual responses.

The nature of the visual stimuli evoking smooth pursuit were was studied using open-loop visual methods. Superimposition of open-loop position and velocity errors during pursuit maintenance resulted in the generation of eye velocities that indicated that stimulus position as well as stimulus velocity is an important stimulus for the maintenance of smooth pursuit.

The time course and dynamics of uniocular saccadic adaptation were studied in monkeys who were made to adapt to a weakened eye. At first the weakened eye had a hysteresis in orbital position, and an orbital-position-dependent saccadic inaccuracy. Both the hysteresis and the orbital position dependent effects were compensated for in a point by point manner with experience. The results suggest that the oculomotor system has a complicated and sensitive corrective mechanisms for the non-linearity of orbital mechanics. Any physical derangement causes maladjustment of this compensation, which can be adapted in time.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: ZO1 EY 00153-06 LSR

PERIOD COVERED

October 1, 1987, to September 30, 1988

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

Visual Motion and the Stabilization of Gaze

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:	Hubert Kimmig	M.D.	Visiting Fellow	LSR, NEI
	Urs Schwarz	M.D.	Visiting Fellow	LSR, NEI

COOPERATING UNITS *(if any)*

Joshua Wallman	Ph.D.	Professor	CUNY

LAB/BRANCH

Laboratory of Sensorimotor Research

SECTION

Oculomotor Control Section

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
1.8	1.0	0.8

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

Processes important for emmetropization, whereby the optical power of the eye comes to match its size, were examined in developing chicks. The eyes of chicks raised in a low-ceiling environment were significanctly more myopic in the upper field than the eyes of control animals. Most of this effect could be accounted for by selective local increases in the depth of the posterior chamber. This is consistent with the notion that vision plays an active role in sculpting the chick's eye to achieve appropriately focussed retinal images in the different parts of the visual field. The maintenance of stable retinal images was studied in chicks by examining the visual mechanisms responsible for stabilizing the head. The head movements induced by translation or rotation of the surroundings revealed powerful stabilizing reflexes that seem to be mediated by separate mechanisms, e.g., responses to translational disturbances showed none of the naso-temporal asymmetries characteristic of the ocular stabilization mechanisms in birds that deal with rotations of the surroundings. Further, rotational oscillations of the surroundings at high frequencies evoked lateral translations of the head rather than rotations, suggesting that only the translational mechanisms respond over this part of the range. Image stabilization was also studied in monkeys by examining the visual mechanisms underlying their ocular pursuit of small moving targets. The early suppression of ocular pursuit by featured backgrounds, described by Keller & Khan (1986), was shown not to be due simply to the reduced physical salience of the track target: suppression was still seen, albeit reduced, if the path of the target was devoid of features and consisted of a dark band. In fact, suppression was still evident even when the band was 30° wide. Suppression also showed interocular transfer, whereby texture seen only by one eye could suppress pursuit initiated by target motion seen only by the other eye. This indicates that suppression can result entirely from centrally mediated interactions between visual inputs.

DEPARTMENT OF HEALTH AND HUMAN SERVICES · PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: ZO1 EY 00152-06 LSR

PERIOD COVERED

October 1, 1987, to September 30, 1988

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

Adaptive Changes in Saccadic Innervation

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

PI:	Lance Optican	Ph.D.	Res. Biomedical Engineer	LSR, NEI
Others:	Zoi Kapoula	Ph.D.	Guest Researcher	LSR, NEI
	Michael E. Goldberg	M.D.	Chief, NMS	LSR, NEI
	David M. Waitzman	M.D.	Staff Fellow	LSR, NEI
	Terence P. Ma	Ph.D.	Post-Doctoral Fellow	LSR, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Sensorimotor Research

SECTION

Oculomotor Control Section

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.3	1.9	0.4

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

Saccades are the rapid eye movements used to change visual fixation. These eye movements are very accurate and end without drift. One of the projects in this lab has studied the ability of the brain to control post-saccadic ocular drift in both eyes. We have found that human subjects, like monkeys, respond to optically-induced post-saccadic slip by developing post-saccadic ocular drift in a compensatory direction. This suggests that after normal saccades there should be no post-saccadic drift. However, normal subjects usually show post-saccadic ocular drift in one or both eyes after every saccade. Attempts to cause monocular adaptation failed, suggesting that the drift after saccades in normal subjects can not be corrected because of the lack of an independent mechanism for each eye.

Another study in this lab has focussed on the neural mechanisms of the sensory-to-motor transformation needed to turn visual target information into saccadic eye movements. It has long been known that the superior colliculus (SC) in the brain stem contains both visual and motor maps related to saccadic eye movements. Up until now it has been assumed by all that the colliculus was providing a static command signaling the change of eye position that would get the eye on target. This leaves unresolved the issue of how the command signal is transformed from a location, or cell-code in SC into the frequency/duration code needed by the eye muscles. Based on new experimental analyses of SC activity patterns, we have formulated a radical new hypothesis of SC function. According to this hypothesis, the SC is the source of the dynamic motor error signal in a local feedback loop controlling saccades. By placing it in the loop, the SC is now shown to be part of the transformation from cell-coded to frequency/duration-coded signals. This radical new hypothesis has far reaching consequences for how we think about the neural control of saccadic eye movements.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: ZO1 EY 00045-10 LSR

PERIOD COVERED
October 1, 1987, to September 30, 1988

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:	Caroline Kertzman	Ph.D.	IRTA	LSR NEI
	Richard Sherins	M.D.	Res. Endocrinologist	NICHD
	Irene Litvan	M.D.	Clinical Fellow	NINCDS
	Edmond FitzGibbon	M.D.	Sr. Staff Fellow	LSR NEI
	James Carl	M.D.	Sr. Staff Fellow	LSR NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Sensorimotor Research

SECTION
Visuomotor Integration Section

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
2.3	1.5	0.8

CHECK APPROPRIATE BOX(ES)

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

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

We have studied the neural mechanisms of visual spatial attention in humans and monkeys. Both species fixated on a spot of light and responded with their hands to peripheral visual targets. Reaction times were faster for targets preceded by a light (cue) on the same side (validly cued) than when the cuing light was on the opposite side (invalidly cued). The performance of the monkeys was selectively altered by injection of transmitter-related drugs into the superior colliculus. Neurons recorded from the colliculus while the monkey performed this task responded well to both the cue and target when they were in the visual receptive field. For some cells when the cue was placed outside of the visual receptive field, the neuron still discharged (weakly) as if it were influenced by the movement of attention through its receptive field.

We tested a population of males treated for Kallmann's syndrome. All responded faster than did age-matched control subjects. The controls were only able to equal the patients' performance when highly motivated. A subset of patients have synkinesis. This group performs the task as do subjects with lesions of parietal cortex. They are very slow responding to invalidly cued targets to one side and responding to any targets after diffuse cues. Such data suggest that these patient have an undiagnosed dysfunction of the parietal cortex.

When patients with progressive supranuclear palsy are tested, they are substantially slower in all respects compared to control subjects. They have significantly increased differences between valid and invalid reaction times suggesting a slowing of the movement of attention. They are able to move their attention vertically as well as horizontally, even though they cannot make vertical eye movements. Treatment with physostigmine, a cholinesterase inhibitor, reduces the difference in reaction times suggesting an improvement in the ability to move attention. The therapy had no effect on the oculomotor capacity of the patients.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER: ZO1 EY 00109-08 LSR

PERIOD COVERED
October 1, 1987, to September 30, 1988

TITLE OF PROJECT *(80 characters or less. Title must fit on one line between the borders.)*
Visuomotor 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:	Hidehiko Komatsu	Ph.D.	Visiting Scientist	LSR, NEI
	Dwayne S. G. Yamasaki	Ph.D.	Guest Researcher	LSR, NEI
	Jean-Pierre Roy	M.D. Ph.D.	Guest Researcher	LSR, NEI
	David M. Waitzman	M.D., Ph.D.	Staff Fellow	LSR, NEI
	Terence P. Ma	Ph.D.	Guest Researcher	LSR, NEI
	Lance M. Optican	Ph.D.	Res. Biomed. Engineer	LSR, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH
Laboratory of Sensorimotor Research

SECTION
Visuomotor Integration Section

INSTITUTE AND LOCATION
NEI, NIH, Bethesda, Maryland 20892

TOTAL MAN-YEARS:	PROFESSIONAL:	OTHER:
4.3	2.7	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 continued our study of the visuomotor processing in the brain for the generation of smooth pursuit and saccadic eye movements. In the study of smooth pursuit eye movements, we concentrated on an area of cerebral cortex devoted to the analysis of visual motion, MST. We found that by stimulating this area during pursuit, we produced an acceleration toward the side of the brain being stimulated. Added to our previous observations, these experiments have localized the brain region related to the maintenance of pursuit eye movements. We also determined that recovery of pursuit following damage to these areas was minimally affected by visual experience during the recovery period. In the study of saccadic eye movements, we identified a type of neuronal discharge in the superior colliculus that indicated that some cells in this structure receive information about how far the eye has moved during a saccade. This led to a reformulation of the role of the superior colliculus in the generation of saccadic eye movements, and a new model of saccadic control.

DEPARTMENT OF HEALTH AND HUMAN SERVICES - PUBLIC HEALTH SERVICE

NOTICE OF INTRAMURAL RESEARCH PROJECT

PROJECT NUMBER

Z01 EY 00244-01 LSR

PERIOD COVERED

October 1, 1987, to September 30, 1988

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

Oculomotor and visual disorders 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:	Edmond J. FitzGibbon	M.D.	Senior Staff Fellow	LSR, NEI
	Michael E. Goldberg	M.D.	Chief, NMS	LSR, NEI

COOPERATING UNITS *(if any)*

LAB/BRANCH

Laboratory of Sensorimotor Research

SECTION

Neuro-Ophthalmologic Mechanisms Section

INSTITUTE AND LOCATION

NEI, NIH, Bethesda, Maryland 20892

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

CHECK APPROPRIATE BOX(ES)

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

☐ (a1) Minors

☐ (a2) Interviews

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

Eye movements were studied in patients with progressive supranuclear palsy. These patients were found to have abnormalities in fixation, pursuit and saccadic eye movements, with an uncoupling of the major trajectories of the horizontal and vertical components of oblique saccades. Vertical eye movements appeared possible only when the horizontal system made small square wave jerks.

Patients with a variety of forms of nystagmus were evaluated in an ongoing study of the clinical significance of the nystagmus waveform.

Eye movement recordings were also used to document early neurologic involvement in patients with xeroderma pigmentosum.

ANNUAL REPORT
NATIONAL EYE INSTITUTE
October 1, 1987 - September 30, 1988

REPORT OF THE ASSOCIATE DIRECTOR FOR BIOMETRY AND EPIDEMIOLOGY

Daniel Seigel, Sc.D.

Organization:

The Biometry and Epidemiology Program consists of a Clinical Trials Branch, an Epidemiology Branch, and a Biometry Section. Drs. Frederick Ferris III and Robert Sperduto serve as Chiefs of the two Branches, respectively; Dr. Roy Milton is the Head of Biometry. Dr. Daniel Seigel is Associate Director.

Functions:

The Biometry and Epidemiology Program (BEP) has three main functions: research, education, and consultation.

Research is the dominant function. It is the Program's mission to plan, develop, and carry out human population studies concerned with the causation, prevention, and treatment of eye disease and vision disorders, with emphasis on the major causes of blindness. This includes studies of incidence and prevalence in defined populations, prospective and retrospective studies of risk factors, natural history studies, clinical trials, genetic studies, and studies to evaluate diagnostic procedures.

Education: The BEP carries out a program of education in biometric and epidemiologic principles and methods for the vision research community. This program consists of courses, workshops, a fellowship program for ophthalmologists, publications, and consultation and collaboration on research.

Consultation: The Program provides biometric and epidemiologic assistance to National Eye Institute intramural and extramural staff and to vision research workers elsewhere. The assistance ranges from consultation through collaboration as co-investigator.

Research Activities:

Clinical Trials. Two contract-supported, randomized multicenter clinical trials on the treatment of diabetic retinopathy are in progress under BEP scientific management. These are the Early Treatment Diabetic Retinopathy Study (ETDRS) and the Diabetic Retinopathy Vitrectomy Study (DRVS).

The ETDRS was designed to provide a better understanding of the best time to use photocoagulation in the course of diabetic retinopathy. Patients with macular edema, preproliferative retinopathy, and mild or moderate proliferative retinopathy are being studied. Three forms of photocoagulation treatment, ranging from restricted focal treatment to complete panretinal

photocoagulation, are being compared with no photocoagulation. In addition, the study is evaluating the effect of daily administration of aspirin, in a comparison with placebo controls, on the incidence of microvascular and macrovascular complications. The study is also investigating factors associated with the progression of disease. Recruitment was completed in March 1985 with the enrollment of 3,928 patients. In December 1985 the study reported that focal photocoagulation of clinically significant diabetic macular edema substantially reduced the risk of visual loss. It was further reported that focal treatment increases the chances of visual improvement, decreases the frequency of persistent macular edema, and causes only minor visual field losses. Analysis files containing all pre-randomization data have been prepared by the coordinating center. Writing teams of clinical investigators have been formed and are working with these files. Two additional manuscripts have been published in the last year. Drs. Lloyd Aiello and Frederick L. Ferris, III, serve as Co-Chairmen for the ETDRS, and Dr. Richard L. Mowery serves as Project Officer.

The DRVS has recruited a group of patients having a total of 997 eyes eligible for the study: 616 eyes with vision reduced by hemorrhage into the vitreous (group H) and 381 eyes still having useful vision but with serious risk of complications that often lead to retinal detachment (group NR). Follow-up of the NR group ended in mid-1988. Two publications have now appeared from this study. The most recent described the two-year status of eyes in the hemorrhage group. Its most important finding was a higher percentage with good vision in eyes assigned to early vitrectomy. This treatment advantage was particularly apparent for juvenile onset diabetics, possibly because of more active retinopathy. A manuscript on three-year results in group NR eyes has been submitted for publication.

Dr. Sperduto was active in the scientific management of a grant-supported clinical trial, the Prospective Evaluation of Radial Keratotomy Study (PERK), which is designed to evaluate a surgical procedure--radial keratotomy--to correct myopia. Three-year results of the study were published in October 1987.

The Clinical Trials Branch implemented the Krypton-Argon Regression of Neovascularization Study (KARNS) in three pilot clinics in December 1983 to test the examination procedures and data collection forms. The major objective of this randomized clinical trial is to compare krypton laser to argon laser panretinal photocoagulation for treating neovascularization on the optic nerve head caused by diabetic retinopathy. The pilot phase was successfully completed in June 1984 and 29 new clinics were enrolled in KARNS starting in August 1984. As of July 1, 1988, a total of 849 patients had been randomized. This study is unique for the National Eye Institute since the functions for both the coordinating center and the fundus photography reading center are being handled by staff of the Clinical Trials Branch. Another feature of this multicenter trial is that the participating clinics receive no financial reimbursement from the National Eye Institute for their participation. Dr. Ferris and Dr. Chew help direct this study. Dr. Mowery serves as Director of the Coordinating Center.

The Clinical Trials Branch is also participating in the Diabetic Macular Edema Study. This Study is designed to compare two different treatment techniques for diabetic macular edema. The first is the treatment technique

demonstrated to be effective in the Early Treatment Diabetic Retinopathy Study and the second is a "grid" technique that was shown to be effective in a small clinical trial and which has become popular. The Study has eight clinics that have enrolled 155 patients to answer questions raised by the study section review of the initial grant submission. Resubmission of the grant application will occur in late 1988 when early follow-up data on these randomized patients is available. Drs. Chew and Ferris are involved in this project.

Dr. Seigel assisted Dr. Robert Turner in preparation of a grant application for a clinical trial on diabetes control and retinopathy, in Oxford, England. The study has been approved and funded. Dr. Seigel serves as the Institute's representative to the study's Data Monitoring Committee, which had its first meeting in the Spring of 1988.

Dr. Seigel is serving as Project Officer for a randomized trial of sorbinil, a drug manufactured by Pfizer Laboratories. The drug is an aldose reductase inhibitor and has potential for preventing or retarding diabetic neuropathy and retinopathy. The NEI is providing scientific leadership for this multiclinic trial, which is funded by Pfizer. Approximately 500 patients have been randomized to treatment and follow-up which ended in mid-1988.

Kathryn Chantry has been appointed as Project Officer for the statistical contract with the Orkand Corporation. Daniel Seigel serves as alternate Project Officer. The Orkand Corporation provides computer support to several of our scientific projects.

Epidemiology. Patients continue to be recruited for a multicenter case-control study of selected retinal diseases. The study is attempting to identify possible risk factors for branch retinal vein occlusion, central retinal vein occlusion, idiopathic macular holes, rhegmatogenous retinal detachment, and exudative macular degeneration. Cardiovascular risk factors are of special interest. Dr. Sperduto and Dr. Seigel are Co-Chairmen of the study. Dr. Mowery serves as Project Officer. Ms. Rita Hiller, Dr. Chew, and Dr. Tamboli are members of the Project Team.

Clinical reexamination of the original Framingham Eye Study participants for lens and macular changes, and photographic evaluation for macular degeneration, is proceeding under research contracts with Epistat Associates and the University of Wisconsin. The examinations will be completed in FY 88, and a photograph grading system will be completed by March 1989. Dr. Milton is Project Officer and Dr. Ferris is Alternate Project Officer for this Study.

Dr. Tamboli, Dr. Sperduto, and Mr. Marvin Podgor are using the SEER (Surveillance, Epidemiology, and End Result) data to study the incidence of and survival rates for retinoblastoma.

Dr. Sperduto is a Co-Principal Investigator in a joint Indo-American case-control study of aging-related cataracts. The study, which is being conducted in New Delhi, India, completed patient recruitment in December 1987. An Investigators' meeting attended by Drs. Sperduto and Milton and Mr. Podgor was held in Delhi in February 1988. A preliminary review of the data was conducted at the meeting and a more complete analysis of the data is now in progress.

Dr. Sperduto is the Project Officer for the joint Italian-American Case-Control Study of Senile Cataract. The study is designed to identify risk factors for aging-related cataracts. Recruitment of patients into the study began in the Spring of 1987 and is scheduled for completion in the Spring of 1989. Because the study design is similar to that of studies being conducted in Boston, Massachusetts, and New Delhi, India, comparison of results among studies should be possible.

Dr. Sperduto, Dr. Milton, and Dr. Mowery collaborated with Chinese investigators from the Peking Union Medical College in conducting a prevalence survey of cataract in Tibet. The study demonstrated a 60% increase in the prevalence of cataract in Tibet compared with the prevalence in a suburb of Beijing. A poster describing the study was presented at the ARVO meeting.

Dr. Sperduto was the coauthor of papers that described and evaluated systems to quantify cataracts in vivo. The systems use photographic transparencies as standards to grade lens changes at the slit lamp or in color photographs. The systems were found to be highly reproducible and of potential value in cross-sectional and longitudinal studies.

Mr. Podgor and Dr. Sperduto have collaborated with Dr. William Kannel (Boston University) and Dr. Gary Cassel (Wilmer Institute) in an investigation of possible associations of lens changes and the incidence of cardiovascular events among diabetics, using Framingham Eye Study data and follow-up data from the Framingham Heart Study. A manuscript is in preparation.

Ms. Hiller, Dr. Sperduto, Mr. Podgor, Dr. Ferris, and Dr. Wilson collaborated on a paper that used data from the Framingham Heart Study and the Framingham Eye Study to examine the association between diabetic retinopathy and the occurence of cardiovascular events (coronary heart disease, intermittent claudication, congestive heart failure, or stroke) in Type II diabetics. A paper is in press in the American Journal of Epidemiology.

Dr. Sperduto, Mr. Podgor, and Ms. Hiller have collaborated with Drs. Manuel Datiles, Kayoko Kashima, and Paul Edwards of the Clinical Branch on the quantification of measurement error in grading retroillumination photographs of posterior subcapsular opacities. A manuscript is in preparation.

Dr. Milton is collaborating with Dr. David Felson, multipurpose Arthritis Center, Boston City Hospital, in use of Framingham Eye Study data for a study of visual impairment and hip fracture. A presentation was made at the American Federation Clinical Research, and a manuscript is being submitted for publication.

Dr. Sperduto continued his collaboration with Dr. M. Christina Leske in conducting a grant-funded, case-control study of aging-related cataracts. The Boston-based study seeks to identify risk factors for specific types of aging-related cataracts and to develop standardized techniques for diagnosing cataracts. Recruitment for the study will be completed in December 1988.

Dr. Mowery serves as the Project Director for an operations research project being conducted at Aravind Eye Hospital in Madurai, India. The purpose of the three-year study is to investigate which of four approaches is

the most effective in recruiting people to an eye clinic for cataract surgery and which method is most cost effective. Preliminary results were presented at the 1988 ARVO meeting. Dr. Mowery serves on both the Executive and Steering Committees for this project.

The Helen Keller International (HKI) supported "cataract free zone" projects in Peru and Brazil began in December 1986 and were completed in June 1987. Dr. Mowery was involved in monitoring the progress of these studies and reviewing the progress reports for HKI. He visited both Peru and Brazil in 1987 and 1988 to work with the investigators in preparing drafts of their final reports for presentations in November 1987 and posters that were presented in May 1988 at the ARVO meeting.

Education:

Dr. Kupfer and Dr. Mowery presented lectures at the 1988 meeting of the American Association of Pediatric Ophthalmologists on clinical trials and epidemiologic methods for doing clinical research.

During 1987-8, Dr. Ferris and Dr. Chew taught courses at the American Academy of Ophthalmology and several university centers on diabetic retinopathy and macular degeneration.

Dr. Carl Kupfer, Dr. Ferris, Dr. Seigel, Dr. Sperduto and Dr. Milton participated as faculty in the eighth of a series of annual courses on epidemiologic and biostatistical approaches to clinical vision research. Along with four university colleagues and a former BEP associate director, Drs. Theodore Colton, Matthew Davis, Charles Hennekens, Lawrence Rand and Fred Ederer, they presented a three-day course in Sarasota, Florida for clinical investigators just before the 1988 ARVO annual meeting. The course was attended by about eighty people from academic institutions and was well received. Plans are under way for a ninth course in 1989.

Dr. Ferris collaborated with the American Academy of Ophthalmology to prepare a videotape summarizing the clinical implications of the results of the Early Treatment Diabetic Retinopathy on the treatment of diabetic macular edema.

Drs. Seigel and Sperduto supervised the training program for three staff fellows from China: Drs. Jingjing Xu, Lizong Hu, and Li-Qi Tang.

Collaboration and Consultation

Dr. Ferris is a member of the Data, Safety, and Quality Review Board for the Diabetes Control and Complications Trial, National Institute of Arthritis, Diabetes, and Digestive and Kidney Diseases. He is also a member of the DRVS Data Monitoring Committee, and Data and Safety Monitoring Committee of the grant-supported Collaborative Ocular Melanoma Study.

Dr. Milton provided biostatistical and administrative support through consultation and review for several international projects in ophthalmic research, including the US-Indo Science and Technology Initiative programs.

Dr. Mowery served on the NCI's Intramural and Administrative Support Contract Review Committee. He also serves as the Project Director for a data management support contract that serves the needs of all NEI staff.

Mr. Podgor consulted with Dr. Griffin Rodgers, NIDDK on hypertension in sickle cell disease.

Mr. Podgor consulted with Deborah Street, Johns Hopkins University, on sample size estimation for an AIDS case-control study.

Mr. Podgor consulted with Dr. Monique Roy, Clinical Branch, NEI on color vision in normal volunteers.

Dr. Seigel served on an NIH Director's panel on hiring and promotions for epidemiologists and statisticians.

Dr. Sperduto collaborated with Dr. Datiles of the NEI's Clinical Branch on the use of photographic techniques to document the presence and progression of lens opacities. A study was completed that estimated the measurement error and its effect on sample size requirements in clinical studies when two measurement systems were used to quantitate the size of posterior subcapsular opacities as seen in retroillumination photographs.

Dr. Sperduto served as an ophthalmic consultant to NEI's Office of Planning and Reporting.

Dr. Sperduto assisted in preparing a report on long-range planning of the National Eye Institute's cataract program. The report will be used as the basis for the Cataract Program Section of the next report of the National Advisory Eye Council for the period 1990-1992.

Dr. Freidlin consulted with Dr. Datiles on statistical methods for comparing endothelial cells of diabetic and non-diabetic patients.

Dr. Freidlin consulted with Dr. Edwards on the analysis of the computer classification of different types of cataracts. She will be acknowledged in the paper.

Dr. Freidlin collaborated with Dr. Roy on the early results of Aging-Related Macular Degeneration (AMD) Study.

Dr. Freidlin consulted with Dr. Kaiser-Kupfer on lens opacities in patients with bilateral acoustic neurofibromatosis. A manuscript is being prepared.

Professional Activities:

Dr. Milton is a member of the Management Committee for "Current Index to Statistics," representing the American Statistical Association.

Dr. Mowery served as Chairman of the Membership Committee of the Society for Clinical Trials.

Dr. Seigel served on the Editorial Board of two journals: the Archives of Ophthalmology and Statistics in Medicine.

Dr. Sperduto is a member of the Data Monitoring Committee for a grant-supported clinical trial on retinitis pigmentosa.

Dr. Sperduto is a member of the Data Monitoring Committee for the Prospective Evaluation of Radial Keratotomy Study.

Dr. Sperduto serves on the Advisory Committee for the Wisconsin Epidemiologic Study.

Presentations

Dr. Ferris was an invited speaker for a symposium on data monitoring at the Clinical Trials Society meeting.

Dr. Mowery presented a lecture at the Eighth Annual Meeting of the Society for Clinical Trials on quality assurance issues in clinical trials.

Dr. Seigel collaborated with Dr. A. Hillis in writing a talk on surrogate statistics in eye research, given at the Biometrics Society annual meeting. It is in press in Statistics in Medicine.

Dr. Seigel presented a lecture to ophthalmology residents at Howard University on the principles of clinical research.

Drs. Seigel and Milton reported on their Monte Carlo analyses of grading systems for lens opacities, making presentations at Johns Hopkins School of Medicine and at NIH. A manuscript summarizing the results has been submitted for publication.

Publications:

1. Aiello LN, Ferris FL. Photocoagulation for diabetic macular edema (Letter to the Editor). Arch Ophthalmol 1987;105:1163.

2. Chylack LT, Leske MC, Sperduto RD, Khu P, et al. Lens opacities classification system. Arch Ophthalmol 1988;106:330-4.

3. Datiles MB, Edward PA, Kaiser-Kupfer MI, McCain L, Podgor M. A comparative study between the PAM and the laser interferometer in cataracts. Graefe's Arch Clin Exp Ophthalmol 1987;225:457-60.

4. Datiles M, Podgor M, Edwards P. Reproducibility study on the early cataract detector (Kowa ECD 2000). Ophthalmic Surg (in press).

5. Early Treatment Diabetic Retinopathy Study Research Group. Techniques for scatter and local photocoagulation treatment of diabetic retinopathy: ETDRS Report No. 3. International Ophthalmol Clinics. 1987;27(4):254-64. Little, Brown & Co., Boston.

6. Early Treatment Diabetic Retinopathy Study (ETDRS) Research Group. Photocoagulation for diabetic macular edema. ETDRS Report No. 4. International Ophthalmol Clinics. 1988;28:265-72. Little, Brown & Co., Boston.

7. Hiller R, Sperduto RD, Podgor MJ, Ferris FL, Wilson PWF. Diabetic retinopathy and cardiovascular disease in type II diabetics: the Framingham Heart Study and the Framingham Eye Study. Am J Epidemiol 1988;128:402-9.

8. Hillis A, Seigel D. Surrogate observations in ophthalmologic studies. Statistics in Medicine (in press).

9. Kaufman SC, Ferris FL, Swartz M, DRS Research Group. Diabetic Retinopathy Report No. 11. Arch Ophthalmol 1987;105:8079.

10. Leske MC, Chylack LT, Sperduto RD, Khu P, et al. Evaluation of a lens opacities classification system. Arch Ophthalmol 1988;106:327-9.

11. Leske MD, Chylack LT, Sperduto R, Pennett M and McCarthy D. Progress toward developing a cataract classification system. In: "Developments in Ophthalmology," S. Karger Publisher, Basel/Switz 1987,vol 15,pp 9-15.

12. Milton RC, Mohan M, Sperduto RD. Indo-US Case-control study of senile cataract design and development, in Straub (ed): "Developments in Ophthalmology." S. Karger Publisher, Basel/Switz 1987,vol 15,pp 92-98.

13. Milton RC, Reddy V, and Naidu AN. Mild vitamin A deficiency and childhood morbidity - an Indian experience. Am J Clin Nutr 1987;46:827-9.

14. Nussenblatt RB, Kaufman SC, Palestine AG, Davis MD, Ferris FL. Macular Thickening and Visual Acuity. Measurement in Patients with Cystoid Macular Edema. Opthalmol 1987;94(9):1134-8.

15. Rosner B, Milton RC. Significance testing for correlated binary outcome data. Biometrics 1988;44:505-12.

16. Roy MS, Podgor MJ, Rick ME. Plasma fibrinopeptide A, b-thromboglobulin, and platelet factor 4 in diabetic retinopathy. Invest Ophthalmol Vis Sci 1988;29:856-60.

17. Roy MS, Podgor MJ, Bungay P, Grunberger G, Carl J, Ellis D. Posterior vitreous flourophotometry in diabetic patients with minimal or no retinopathy. Retina 1987;7:170-6.

18. Seigel D. Designs for clinical research. Arch Ophthalmol. Dec 1987;105:1647-9.

CONTRACT NARRATIVE

Thirteen Clinical Centers; a Coordinating Center at the University of Minnesota, Minneapolis, Minnesota; and a Fundus Photograph Reading Center at the University of Wisconsin, Department of Ophthalmology, Madison, Wisconsin.

Title: Diabetic Retinopathy Vitrectomy Study (DRVS)

Principal Investigators: Matthew D. Davis, M.D. (Study Chairman)
Daniel Seigel, Sc.D. (Project Officer)

Current Fund Allocation: $144,966 (estimate) FY 1988 (EY 5 2148, EY 5 2147)

Objectives: The DRVS is a multicenter clinical trial to:

1. Evaluate vitrectomy performed in the first six months after severe vitreous hemorrhage secondary to diabetic retinopathy compared to the more usual practice of waiting twelve months after vitreous hemorrhage to remove the vitreous (group H).

2. Evaluate vitrectomy in eyes with good vision but with severe proliferative retinopathy and poor prognosis before vision is lost through hemorrhage or retinal detachment (group NR).

3. Study the natural history of severe proliferative diabetic retinopathy.

Major Findings: The first report of results for eyes with severe vitreous hemorrhage was published in the November 1985 issue of the Archives of Ophthalmology. Over six hundred eyes with recent severe diabetic vitreous hemorrhage were randomly assigned to either early vitrectomy or deferral of vitrectomy for one year. After two years of follow-up, 25% of the early vitrectomy group had visual acuity of 10/20 or better compared with 15% in the deferral group.

Significance to Biomedical Research and the Program of the Institute: Diabetic retinopathy is one of four major causes of adult blindness and differs from the other three (macular degeneration, glaucoma, cataract) in that it generally affects a younger population. Vitrectomy has the theoretical potential of removing the "scaffolding" on which abnormal new vessels can develop, fibrous tissue can form, and retinal detachment can occur. It is important to determine when such intervention is most likely to deter this process and reduce the incidence of loss of vision.

Proposed Course: Follow-up has been completed. A manuscript has been submitted on 3-year results in the NR series. In 1988, 4-year results in the hemorrhage series will be analyzed.

NEI Research Program: Retinal and Choroidal Diseases

Publications:

The Diabetic Retinopathy Vitrectomy Research Group. Two-year course of visual acuity in severe proliferative diabetic retinopathy with conventional management. DRVS Report No. 1. Ophthalmology, 92:492-502, 1985.

The Diabetic Retinopathy Vitrectomy Study Group. Early vitrectomy for severe vitreous hemorrhage in diabetic retinopathy. Two year results of a randomized trial. Diabetic Retinopathy Vitrectomy Study Report Number 2. Arch Ophthalmol 103:1644-1652, 1985.

CONTRACT NARRATIVE

Twenty-three Clinical Centers; a Coordinating Center at Maryland Medical Research Institute; a Fundus Photograph Reading Center at the University of Wisconsin, Department of Ophthalmology, Madison; a Central Laboratory at the Centers for Disease Control, Atlanta, Georgia; and an Electrocardiogram Reading Center at the University of Minnesota, Minneapolis, Minnesota.

Title: Early Treatment Diabetic Retinopathy Study (ETDRS)

Principal Investigators: Dr. Lloyd Aiello (Co-Chairman)
Dr. Frederick L. Ferris, III (Co-Chairman)
Dr. Richard L. Mowery (Project Officer)

Current Fund Allocation: $5,696,686 (estimated) for FY 1988

Objectives: The Early Treatment Diabetic Retinopathy Study (ETDRS) is a multicenter randomized clinical trial, the main goals of which are:

1. To determine whether treatment of early stages of proliferative and nonproliferative diabetic retinopathy, with or without macular edema, by aspirin and/or prompt photocoagulation is effective in decreasing the rate of development of known retinopathy risk factors and/or the development of severe visual loss when compared to placebo or deferred photocoagulation.

2. To help determine the best time to initiate photocoagulation treatment in diabetic retinopathy.

3. To monitor closely the effects of diabetes mellitus and/or of photocoagulation on visual function.

4. To produce natural history data that can be used to develop (identify risk factors) and test etiologic hypotheses in diabetic retinopathy.

Major Findings: From April 1980 to March 1985, the ETDRS research group enrolled 3,928 diabetic patients with early proliferative retinopathy, moderate to severe nonproliferative retinopathy, and/or diabetic macular edema in each eye. In December 1985, the research group published a report that focal photocoagulation of "clinically significant" diabetic macular edema substantially reduces the risk of visual loss. Focal treatment also increases the chance of visual improvement, decreases the frequency of persistent macular edema, and causes only minor visual field losses.

Significance to Biomedical Research and the Program of the Institute: The National Eye Institute regards fostering careful evaluation of new and widely used ophthalmic treatments as an essential element in its mission. This study represents an extension of the Institute's interest in preventing visual impairment of patients with diabetes.

Proposed Course: The study will end patient follow-up in July 1989 and prepare reports at that time on study results.

NEI Research Program: Retinal and Choroidal Diseases

Publications:

Early Treatment Diabetic Retinopathy Study Research Group: Photocoagulation for Diabetic Macular Edema. Arch Ophthalmol 103:1796, 1985.

Early Treatment Diabetic Retinopathy Study Research Group: Photocoagulation Therapy for Diabetic Eye Disease. JAMA 254:3086, 1985.

Early Treatment Diabetic Retinopathy Study Research Group: Treatment Techniques and Clinical Guidelines for Photocoagulation of Diabetic Macular Edema, Report Number 2. Ophthalmology, 94:761-774, 1987.

Early Treatment Diabetic Retinopathy Study Research Group: Techniques for Scatter and Local Photocoagulation Treatment of Diabetic Retinopathy : Early Treatment Diabetic Retinopathy Study Report No. 3. Internat Ophthal Clinics, 1987;27(4):254-64. Little, Brown & Co. Boston.

Early Treatment Diabetic Retinopathy Study (ETDRS) Research Group: Photocoagulation for Diabetic Macular Edema. ETDRS Report No. 4. Internat Ophthalmol Clinics, 1988;28:265-72. Little, Brown & Co. Boston.

Ferris FL and Aiello LM: Photocoagulation for Diabetic Macular Edema. Letter to the Editor. In press.

CONTRACT NARRATIVE

Five Clinical Centers; a Central Laboratory at National Health Laboratories, Vienna, Virginia; a Nutrition Biochemistry Laboratory at Centers for Disease Control, Atlanta, Georgia; an Electrocardiogram Reading Center at the University of Minnesota, Minneapolis, Minnesota; a Data Management Group at Rockville, Maryland.

Title: Eye Disorders Case Control Study (EDCCS)

Principal Investigators: Dr. Daniel Seigel (Co-Chairman)
Dr. Robert Sperduto (Co-Chairman)
Dr. Richard Mowery (Project Director)

Current Fund Allocation: $801,075 (estimated) for FY 1988

Objectives: The goal of the Eye Disorders Case Control Study is to evaluate the role of potential risk factors for a number of disorders of the eye for which adequate epidemiologic data are now lacking. Secondary objectives of the study are to evaluate grading systems, particularly for hypertensive and arteriosclerotic changes in the retina.

Major Findings: Pilot testing at each of the four clinical centers was done between February-May 1986 based on the Manual of Operations designed by the NEI staff and the clinic staffs. Each clinic recruited at least five patients. The main study began in June 1986. Over 700 cases and 400 controls have been recruited. Wilmer Eye Clinic at Johns Hopkins Hospital has been added as a fifth clinic.

Significance to Biomedical and the Program of the Institute: In the 1983 Report of the National Advisory Eye Council, a need was identified for "epidemiologic studies on various types of retinal vascular disease with particular view to isolating causative factors." In recent years, careful epidemiologic studies have been initiated for diabetic retinopathy, aging-related macular degeneration and ocular melanoma. However, for various forms of retinal artery and vein occlusions and rhegmatogenous retinal detachments, high quality epidemiologic data are lacking. In particular, cardiovascular risk factors appear to be associated with these disorders. This study represents an extension of the Institute's interest in identifying risk factors associated with retinal diseases.

Proposed Course: The five clinical centers will continue to recruit both cases and controls for four years. As soon as at least two hundred cases have been examined in any one disease group, analyses will begin.

NEI Research Program: Retinal and Choroidal Diseases

Publications: None

CONTRACT NARRATIVE

A Fundus Photograph Reading Center at the Department of Ophthalmology, University of Wisconsin, Madison

Title: Reading Center for Framingham Eye Study Photographs

Principal Investigators: Matthew D. Davis, M.D. (Principal Investigator)
Roy C. Milton, Ph.D. (Project Officer)
Frederick L. Ferris, III, M.D. (Alternate Project Officer)

Current Fund Allocation: $75,838 (estimated) FY 1987 for EY 62116

Objectives: To develop a classification system for aging-related macular disease and to provide an evaluation of that disease using the fundus photographs from the 1973-1975 Eye Study and the fundus photographs to be taken in the 1986-1988 Framingham Eye Study.

Major Findings: This study began in June 1986 and is a companion study to The Ocular Re-examination of Framingham Eye Study Subjects. Development of the classification system is complete and application is ongoing.

Significance to Biomedical Research and the Program of the Institute: Aging-related macular degeneration is a major cause of blindness. Incidence rates for this disease are not available, and the natural history is largely unknown. The data from this study on incidence, progression, and association with other variables could lead to an increased understanding of this aging-related ocular disease and possibly to the development of measures to prevent or delay its onset. This study is consistent with the Institute's interest in epidemiologic research and in alleviation of the human and economic burden of eye disease.

Proposed Course: The classification scheme for aging-related macular degeneration will be applied to approximately 1500 fundus photographs from the 1973-75 study and 1000 fundus photographs to be taken during 1986-88. Quality control and monitoring of evaluation methods and results will be ongoing. Photograph classification will be completed by March 1989.

NEI Research Program: Retinal and Choroidal Diseases

Publications: None.

CONTRACT NARRATIVE

A clinical Examination Center at Framingham, Massachussetts, operated by Epistat Associates, Incorporated.

Title: Ocular Re-examination of Framingham Eye Study Subjects

Principal Investigators: Theodore Colton, Sc.D. (Principal Investigator)
Lawrence Rand, M.D. (Co-Investigator)
Roy C. Milton, Ph.D. (Project Officer)
Frederick L. Ferris, III, M.D. (Alternate Project Officer)

Current Fund Allocation: $240,266 (estimated) for FY 1988 EY 2105

Objectives: This re-examination of Framingham Eye Study subjects, first seen in 1973-1975, is an epidemiologic study of aging-related macular degeneration and cataract to determine their incidence, to describe their natural history, and to identify associations between their presence or progression and variables in the Framingham Heart Study, whose values were determined before development or progression of these diseases.

Major Findings: This study began in January 1986. Study procedures have been developed, equipment has been purchased and installed, and examination staff have been hired and trained. Examination of study subjects began in August 1986. About 1000 subjects will be examined during the study, and examinations will be completed by December 1988.

Significance to Biomedical Research and the Program of the Institute: Aging-related macular degeneration and cataracts are major causes of blindness in the United States, accounting for thirteen and nine percent of all blindness, respectively. Incidence rates for these diseases are not now available, and their natural history is largely unknown. The data from this study on incidence, progression, and association with other variables could lead to an increased understanding of these aging-related ocular disease and possibly to the development of measures to prevent or delay their onset. This study is consistent with the Institute's interest in epidemiologic research and in alleviation of the human and economic burden of eye disease.

Proposed Course: Examination of an estimated 1000 study subjects will be completed by December 1988. Quality control procedures and monitoring of data is ongoing.

NEI Research Program: Retinal and Choroidal Diseases

Publications: None