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ABSTRACT

Presented is an annual report of research and supported by the National Eye Institute (NEI) during the 1974 fiscal year. It is explained that the purpose of NEI research programs is to develop scientific knowledge which can be applied to the improved prevention, diagnosis, and treatment of visual disorders. The section on extramural and collaborative programs focuses on research relating to retinal and choroidal diseases, corneal diseases, cataract, glaucoma, and sensory-motor disorders and rehabilitation. Described in the section on intramural research are programs of the Clinical Branch (such as laboratory study of ocular disease in patient); projects of the Laboratory of Vision Research related to biochemistry, experimental embryology, experimental pathology, and neurophysiology; activities of the Office of Biometry and Epidemiology related to diagnostic methods, incidence of disease, identification of risk factors, and comparison of alternative treatments; and public information and program planning efforts. Also included are lists of references or publications (given at the end of each subsection) and a list of intramural research projects. (LH)

EC

The National Eye Institute

annual report

FY 1974

ANNUAL REPORT
NATIONAL EYE INSTITUTE
July 1, 1972 - June 30, 1973

PREFACE

Progress against leading causes of blindness and visual disability in the United States is highlighted in this report of research conducted and supported by the National Eye Institute during FY 1973.

Now in its fifth year, the NEI has formally begun to take stock of past accomplishments, assess the comprehensiveness and effectiveness of its current programs, and document the requirements for the future development of vision research support. Preliminary analysis during FY 1973 of its five major programs by a Committee of the National Advisory Eye Council has shown that although balance in these programs is generally good, there is need for greater emphasis in certain key areas of research in order to hasten the development of knowledge which can be applied to the improved prevention, diagnosis, and treatment of visual disorders.

In addition, the support of manpower training must be maintained and increased in order to sustain the high level of achievement that characterizes vision research in this country today. Without a consistent program of training support, the research momentum gained through the creation of the Eye Institute will be inevitably slower.

Continued emphasis on the support of quality laboratory research, application of epidemiological techniques to eye disease problems, and stimulation of additional clinical research, particularly in retinal and uveitial diseases, will help provide the scientific base upon which more effective vision care and eye disease prevention programs can be built. In this manner, the National Eye Institute approaches its goal of reducing the enormous toll in human suffering and economic loss taken each year in our nation in blindness and visual disability.

Karl Kupfer, M.D.
Director
National Eye Institute

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[illegible] OF THE ASSOCIATE DIRECTOR FOR
[illegible] AND COOPERATIVE PROGRAMS

A. Fiscal Year 197[illegible] Funding

1. Research Grants

During the past year the Institute has endeavored to realize three major objectives in [illegible] research grants: a. to support the largest possible number of high quality research projects through prudent program and fiscal management of available resources, b. to minimize harmful fluctuations in funding patterns and c. to insure an adequate level of support for new research efforts as well as maintain a balanced program of on-going research.

The release of $[illegible],000 in supplemental FY 197[illegible] funds, as well as an increase of $[illegible],000 over the original FY 197[illegible] budget estimates has enabled the Institute to accomplish these objectives without implementing a policy of fiscal [illegible] which could jeopardize the further development of research in the visual sciences. The total funding distribution awarded with supplemental funds is shown below.

[illegible] Grant Support
[illegible] in Thousands

	Number	Total Amount Awarded
Prior year commitments	[illegible]	$[illegible],[illegible]
Competing renewals	[illegible]	$[illegible],[illegible]
New awards	[illegible]	$[illegible],[illegible]
Total	[illegible]	$[illegible],[illegible]

In addition to the support of regular research grants, the Institute has initiated a "new [illegible]" program, called the NEI Special Visual Sciences Research Award Program.

The program is designed to encourage newly-trained investigators to remain active in eye research during the formative stages of their career. The awards are made for a [illegible]-year period of up to three years. Direct costs will be awarded in amounts up to $[illegible],000 per annum, and may be used for such items as [illegible] supplies, or technical support services. The first applications for this program were reviewed at the March [illegible] meeting of the National [illegible] Eye Council.

2. Training Programs

Although the Administration's decision to phase out the current training grant program is being implemented, the FY 1974 appropriation, together with the release of FY 1973 impounded funds, has enabled the Institute to award a total of 49 training grants at a support level of $1,857,000, including $454,000 of impounded funds, for 6 competing applications.

Fellowship support continued in the amount of $362,000 for commitments for 12 awards made prior to the phaseout of training programs, plus $1,300,000 for the support of 65 competing awards.

3. Research Contracts

During FY 1974, 19 contracts were funded at a total cost of $2,200,000. Seventeen of these were exclusively for the Institute's collaborative study to evaluate treatment modalities for diabetic retinopathy. The remaining contracts were awarded for "The Development of a Large-Scale Method for the Preparation of Rod Outer Segments" and "The Biostatistical Analysis of Data Obtained from the Glaucoma Collaborative Study."

B. Organization and Staffing

1. Program Structure

Over the past year, the Extramural programs have been restructured to reflect more accurately the Institute's program priorities. The new major program areas, with estimates of FY 1974 support levels for research grants are as follows:

Program	FY 1974 Research Grant Funds
1. Retinal and Choroidal Diseases	$9,687,000
2. Corneal Diseases	5,148,000
3. Cataract	2,718,000
4. Glaucoma	3,348,000
5. Sensory-Motor and Rehabilitation	6,604,000

To achieve this programmatic orientation at the operating level, program directors have been assigned on the basis of the revised structure, and will be responsible for coordinating both contract and grant supported research in their designated programs. Similarly, the responsibilities of management personnel in the Contracts and Grants Branch have been revised to reflect the same program management framework.

2. National Advisory Eye Council

In order to establish a sound basis for Institute program planning activities in each program area, a subcommittee of the National Advisory Eye Council has been established to review current research support and, with the advice of scientific and technical experts in specific program areas, formulate recommendations regarding program balance to be transmitted to the full Council. Review of all programs is expected to be completed by November 1974.

3. Vision Research Program Committee

As part of the recent review of Federal advisory committees, the Institute proposed to eliminate training grant and fellowship review from the functions of the Vision Research and Training Committee, and broaden its sphere of activity to include not only the review of special project grant applications, but also participation in the analysis of extramural programs and in advising the Institute in its support of specific research areas. It was also proposed that the committee be renamed the Vision Research Program Committee, and a revised charter reflecting these changes was approved by the Secretary, HEW.

4. Establishment of Data and Analysis Unit

In response to increased data requirements for analysis, reporting, and management of Institute programs, a data and analysis unit has been established in the Office of the Associate Director. Initial efforts have begun to develop a comprehensive information system which will serve as a resource for extramural operations as well as provide analytical data for program planning, budget formulation, and reports.

5. Staff Changes

The following personnel have been appointed to key positions in the Extramural and Collaborative Programs during the past year:

Dr. Wilford L. Nusser	Chief, Scientific Programs Branch and Acting Program Director, Glaucoma Program
Dr. Luigi Giacometti	Program Director for Cataract and Corneal Disease Program
Dr. Israel A. Goldberg	Assistant to Acting Program Director, Glaucoma Program
Dr. John B. Mathis	Program Director for Sensory-Motor and Rehabilitation Program

RETINAL AND CHOROIDAL DISEASES

The NEI Retinal and Choroidal Diseases Program is divided into six disorder areas: Circulatory Abnormalities, Vitreous Degeneration and Retinal Detachment, Developmental and Degenerative Abnormalities, Maculopathies, Tumors, and Uveitis.

CIRCULATORY ABNORMALITIES

These disorders, which may be due to environmental influences or heredity, include development, obliteration, tortuosity, occlusion of blood vessels, and hemorrhage. They may include such clinical diseases as retrolental fibroplasia, diabetic retinopathy, and macular degeneration.

Preretinal vitreous monitoring of oxygen has been proposed as a useful method of studying a variety of conditions of retinal toxicity and degeneration in which retinal blood flow is an important factor. Dr. Noble David and associates[1,2,3] at the University of Miami have continued to use fluorescein densitometry for studying the relationship of blood oxygenation to retinal blood flow. The rhesus monkey has served as the animal model in which constriction of major retinal arteries and veins during hyperoxia and dilation during hypoxia were demonstrated. Retinal blood flow increased considerably in hypoxia and showed a moderate decrease in hyperoxia. These findings indicate that the retinal circulation parallels that of the brain in adjusting to changes in the arterial oxygen partial pressure (pO_2) with compensatory changes in blood flow. These investigators continue to apply techniques for quantitative measurement of relative retinal blood flow compared to such variables as blood pressure, blood volume, hemorrhagic shock, and optic nerve atrophy.

The pathogenesis factors which determine the evolution of different vascular patterns and techniques of altering hemodynamics to prevent retinal complications in patients with branch retinal vein obstruction are being studied by Dr. Frank W. Newell and his colleagues[4,5] at the University of Chicago. The retinal vasculature of patients in these studies have been followed for periods of up to five years utilizing fundus photography, fluorescein angiography, and measurement of arterial perfusion pressure. The long-term fluorescein angiographic assessment and vascular dynamics of these patients indicate that they can be classified into four major groups: Group I includes patients in whom arterial perfusion pressure, retinal circulation time, and visual functions remain normal; Group II includes patients in whom arterial perfusion pressure is normal, but there is some delay in the retinal circulation time; Group III includes patients who demonstrate an impaired arterial perfusion and retinal circulation time demonstrating marked venous stasis; and Group IV includes patients in whom arterial perfusion is grossly impaired and retinal circulation time shows gross venous stagnation.

Careful quantitation of an experimental model of retinal eschemia and vascular proliferation may assist in the identification of factors associated with retinal vascularization and proliferation. Dr. Arnall Patz and associates[6] at Johns Hopkins Medical School are conducting a study to determine the optimal pO_2 levels associated with production of retinal capillary and small vessel

non-perfusion. The response is relatively linear up to a pO_2 of approximately 300 mm Hg. Sustained pO_2 levels in this range produced changes with the severity of capillary non-perfusion, as determined by fluorescein angiography, corresponding to the degree of retinal ischemia produced.

In the course of study of retinal blood flow in choroidal and retinal vasculatures, Dr. Arnall Patz[7,8] and associates, in collaboration with the Applied Physics Laboratory at Johns Hopkins University, have demonstrated that indocyanine green dye will permit infrared absorption angiography of the choroidal filling. The limitations of fluorescein dye are eliminated by use of indocyanine green. The application of infrared absorption angiography to the simultaneous study of choroidal and retinal circulation is in progress and will permit an investigation of the contribution of the choroidal and retinal circulation to retinal oxygenation. Routine choroidal circulation can be observed through simultaneous photography of choroidal and retinal circulations. Swelling of the optic cup, called papilledema, has been produced in experimental models by the use of intracranial surgery. Dr. Mark O. Tso[9] and associates at the Armed Forces Institute of Pathology have been using experimental models created by increasing intracranial pressure nonsurgically or by lowering intraocular pressure. The mechanism of breakdown of the optic nerve-blood barrier in the optic disc is currently being studied. The leakage of fluid from the vasculature of the optic disc and possible from the peripapillary choroidal plexus in papilledema is being investigated by use of histochemical techniques which employ horseradish peroxidase as a tracer substance. Intravascular injection of this enzyme as a tracer will show areas of localized disruption of blood-optic nerve barrier.

The animal model for papilledema has been produced by x-irradiation of the right occipital lobes of rhesus monkeys. Of thirteen monkeys irradiated, four developed full papilledema, three showed mold edema of the optic disc while the remaining six developed atrophy of the optic disc. Those animals with papilledema also showed an increase in intracranial pressure. Electron microscopic study of the optic disc of animals with papilledema demonstrated swelling as well as fluid accumulation in the intercellular space. Extension of this work by use of animal models will be of assistance in understanding the pathogenesis of papilledema. The relationship between the peripapillary choroidal and the central retinal circulations with increases in intracranial pressure or decreased intraocular tension may be defined.

Dr. David J. Apple[10] and associates at the University of Illinois have designed a study to analyze the efficiency of argon laser burns of blood vessel closure or obliteration and to analyze factors relating the movement of fluid between various retinal and choroidal components. Monkeys have been subjected to photocoagulation treatment with subsequent histopathological and electron microscopic analyses. The results show that specificity of vascular effects ascribed to the argon laser is unfounded. The investigators have never found a destroyed or occluded vessel in the absence of significantly destroyed nerve fiber layer parenchyma. In addition, choriocapillaris closure has been a constant finding.

VITREOUS DEGENERATION AND RETINAL DETACHMENT

These disorders include rhegmatogenous and other retinal detachments due to vitreous fiber formation and shrinkage, and vitreous liquification and opacification.

Chemical Development

An increased understanding of the biological role of hyaluronic acid in the vitreous may lead to the possible use of this biopolymer to control inflammation and regenerative processes. Further characterization of the structure of hyaluronic acid in solution and as a solid could be important in the possible therapeutic use of hyaluronic acid. In addition, the vitreous is useful in the study of biosynthesis of biopolymers. It may be viewed as a simple connective tissue. Dr. Endre A. Balazs[11] and associates at the Boston Biomedical Research Institute have been studying enzymes involved in the synthesis of vitreal components. They have also been investigating the role of salts such as sodium chloride on the swelling properties of vitreous gel. It has been suggested that the biopolymers may serve as volume regulators for gels such as vitreous.

Membrane Development

Investigation of vitreous membrane formation development as a consequence of hemorrhage and intraocular inflammation is in progress under Dr. David A. Swann[12] and associates at the Retina Foundation in Boston. They find that vitreous membranes may develop because of plasma clotting or aggregation of platelets. This group of investigators has conducted studies which document the effects of injecting platelets with or without plasma into the vitreous cavity. It now appears that when blood components are released into the vitreous cavity, intact platelets play a role in the instantaneous formation of membranes. The vitreous membranes can be formed in the absence of plasma proteins provided the platelets are physiologically functional. In some respects, platelet membranes resemble vitreous floaters which are seen clinically. Platelet-induced membranes are not accompanied by a proliferation of fibroblasts and fibroblastic membranes which may lead to retinal detachment.

Enucleated human eyes are being examined by Dr. Robert Y. Foos[13] and associates at UCLA. He has observed a prevalence of proliferative vitreoretinopathies which resulted from complications of ocular disease or surgery. This high incidence indicates the need for a better understanding of the underlying events and the relationship of these events to more complex lesions which lead to blindness. The proliferative lesions at the juncture of the vitreous and retina range from simple epiretinal membranes to processes in which both fibrous and vascular components lead to retinal detachment. Epiretinal membranes are delicate strands on the surface of the retina. Their cause is poorly understood and has been the subject of study by Dr. Foos. They are found in association with developmental, inflammatory, vascular, and mechanically produced lesions. The experience in Dr. Foos' laboratory indicates that the membranes originate in the glial cells which become mitotic through a variety of stimuli.

Dr. Miguel F. Refojo[14] and associates at the Retina Foundation, Boston, point out that in cases of severe vitreous traction these is need for a material which will tamponade the retina against the choroid during formation of chorioretinal adhesion and will not pass through a retinal break. Dr. Refojo has been developing synthetic polymers similar to the natural vitreous body of the eye. The gel must be injectable and must not hinder vision by scattering light.

DEVELOPMENTAL AND DEGENERATIVE ABNORMALITIES

Pigment Epithelium

This is a single layer of cells in the retina which contain varying amounts of pigment. These cells are firmly bound to Bruch's membrane which is bound to the choriocapillaris. The intimate relationship between the photoreceptors and their blood supply suggests that the pigment epithelium has a critical role in the maintenance of the photoreceptors. The pigment epithelium has been implicated in clinical problems of maculopathies, retinal detachment, visual pigment synthesis, removal of rod outer segment debris, and information processing as implied by its contribution to the electroretinogram. Due to an awareness of the implications and critical role of the pigment epithelium, new concepts of the pigment epithelium involvement in retinal degenerative disorders are developing.

It is unclear whether the pigment epithelium follows the general biological phenomenon of phagocytosis or whether this structure had additional specializations which are characteristic of these cells. Dr. Joe G. Hollyfield[15] and associates at Columbia University have shown that phagocytic activity begins early in the amphibian embryo and is responsible for the removal of egg pigment which is eliminated from cells of retinal neuroepithelium. These investigators have explored the question of whether the phagocytic activity of the pigment epithelium is specific or an indiscriminate scavenging. The study has shown that pigment epithelial cells will phagocytize polystyrene spheres which have been injected into the space between the retina and pigment epithelium in the frog embryo, tadpole, and adult; and, therefore, the phagocytic activity is not restricted to rod outer segment discs.

The interphotoreceptor matrix appears to be synthesized by the neural retina and the pigment epithelium with possible contributions from the photoreceptors and Muller cells. Dr. Lynette Feeney[16,17] and associates at the University of Oregon Medical School have used radioactive precursors of protein glycoproteins and glycosaminoglycans, which are components of the interphotoreceptor matrix, to produce autoradiographs in an attempt to v rify the site of matrix macromolecules. Autoradiographs of 10-day old and adult mice were prepared for light and electron microscopy. Pulse label techniques show that although the apical microvilli and their cell coats in the 10-day old mice are proliferating maximally, the adult microvilli show a more intense labelling which probably relates to increased phagocytic activity.

Most of the studies of pigment epithelium have involved embryonic eyes as a source of explants or in situ observations of phagocytosis, proliferation, or cell movement. Conclusions with regard to potential activities of these

cells have been based upon histopathologic observations. Dr. Mark O. Tso[18] and associates at the Armed Forces Institute of Pathology collaborated with Dr. Daniel Albert and associates at Yale University and developed a method of organ culture of human pigment epithelium and choroid in an effort to study the reactions of this tissue to various stimuli. These investigators have shown that preparations of human tissue obtained postmortem and during surgical procedures may be maintained in culture for at least two weeks. The tissue does not proliferate or degenerate and appears to remain active and suitable for morphological studies. The culture system employed produced pigment epithelium which resembled the in situ tissue in that there was a persistence of apical villi, terminal bars, infoldings of basal plasma membranes, intact basement membranes, and melanin and lipofuscin granules. The techniques may be useful in studying the cytological behavior of pigment epithelium in vitro during various stages of retinal diseases.

Dr. Kenneth Brown[19,20] and associates at the University of California have concentrated their efforts upon the functional relations of photoreceptors to the pigment epithelium. They have described the anatomic relationship between the pigment epithelial cell and photoreceptors in frog retina. The pigment epithelium forms apical processes which, in the cat, ensheath the cone outer segment. Although the functional significance of this sheath is not understood, it is evident that the pigment epithelial cell relates to the cone as well as the rod. These investigators point to the similarities of the choroid plexuses of the brain and the retinal pigmen epithelium and choroid. A series of intracellular microelectrode experiments indicate differences and similarities in ion permeability and flux at apical and basal membranes of the pigment epithelial cell. Ouabain placed on the epithelial side of the tissue was found to depolarize the apical membrane but was ineffective when placed on the choroidal side. These observations indicate that the apical membrane, but not the basal membrane, contains a sodium-potassium pump. The physical condition of the pigment epithelium used in transport studies is examined by scanning electron microscopy. These in estigators have developed a technique for vertically cracking the epithelial layer at cell junctions so that lateral surfaces of individual cells can be visualized.

Membranes

The production of an electrical response to the absorption of light by photoreceptors is related to a system of light-induced membrane reorganization. Investigation of intact membranes and relevant membrane models may further our knowledge of the mechanism of energy-transduction and transfer in photoreceptor membranes. The structure of photoreceptor membranes and visual pigment properties are the subjects of current investigations.

Dr. Kent Blasie[21] and associates at the University of Pennsylvania have approached the description of membrane structure and light-induced membrane phenomena at the submolecular level. These investigators have determined by x-ray diffraction the location of rhodopsin within the profile of photoreceptor disc membranes, the forces responsible for this location, and the local arrangement of rhodopsin over the surface of the disc membranes. It is anticipated that analysis of diffraction data from the disc membrane profile will

permit a detailed evaluation of lipid-protein interactions in the membrane structure at the submolecular level. To date, data appear to fit a model of anchored photopigment molecules which protrude into the aqueous layer and into the lipid core. Bleaching causes the photopigment to move deeper into the lipid core and in a transmembrane direction.

Dr. Wayne L. Hubbell[22] and associates at the University of California have been interested in the location of rhodopsin in the disc membrane. They have shown that the surface of the rhodopsin molecule is in direct contact with the hydrocarbon chains of the phospholipid of the disc membranes which it penetrates. The distribution of rhodopsin molecules in the plane of the membranes has been studied by techniques which reveal membrane surfaces. It has been found that the rhodopsin behaves as a solute which is regulated in its solution by light. Careful studies by this group indicate that rhodopsin completely traverses the thickness of the membranes. The process by which the light energy is transduced to produce the electrical response may relate to a permeability change in the disc membrane. The model systems of rhodopsin in a phospholipid bilayer permits the investigation of light-activated ion movement in membranes. Results of model membranes appear to be consistent with current interpretations of x-ray studies of intact photoreceptor membranes.

Dr. Richard A. Cone[23] and associates at the Johns Hopkins University are studying the effect of rhodopsin molecule on the general disc membrane characteristics. The rapid lateral diffusion of rhodopsin within the disc membrane has been observed by microspectrophotometric techniques. Their results indicate that the effective viscosity of the membrane permits rhodopsin to float freely in the lipid phase. These investigators find that rod outer segments offer the best model for the study of rapid lateral diffusion of proteins in membranes. By observing diffusion constants or rhodopsin, it will be possible to determine the effective radius of the molecule within the lipid phase of the membrane. This work implies that in the plane of the membrane, the rhodopsin molecule must be slightly elliptical or nearly circular in shape. Rhodopsin may be thought of as a neuronal protein, in a neural membrane, and knowledge of its structure and function will reveal factors which influence transport of drugs, nutritional components, and the spread of electrical energy in photoreception.

The question of rod outer segment disc organization and the localization of rhodopsin have also been investigated by Dr. Edward A. Dratz[24] and associates at the University of California. Preparations of intact discs and rod outer segment fractions were exposed to membrane-permeable and membrane-impermeable reagents which label amino acids. They found that half of the rhodopsin amino groups were labelled by the membrane impermeable reagent. These data indicate that rhodopsin must protrude into the aqueous medium between discs. It seems clear that rhodopsin exposes a hydrophilic surface on the outside of the disc. It is still unclear whether a single rhodopsin molecule transverses the disc membrane or whether rhodopsin molecules are situated on both sides of the membrane. Factors which influence membrane structure and function will be more easily understood as more information about membrane proteins and ion transport is obtained.

Visual Pigments

The question posed is how changes in molecular structure of visual pigment molecules relate with nervous excitation of the photoreceptor. Since structural changes in the photopigments are the first events in the transduction process, comprehension of visual pigment photochemistry will help to understand visual excitation. Correlations between ionization and hydrogen-ion concentration changes of rhodopsin and the late receptor potential have been investigated by Dr. Sanford E. Ostroy[25] and associates at Purdue University. They have isolated thermal intermediates of visual pigment bleaching. Their experiments show proton uptake during illumination and proton release during later processes. These reversable effects implicate hydrogen ion changes in visual adaptation. Furthermore, ionization changes may be a controlling factor for the existence of photopigment intermediates.

Dr. Bruce E. Goldstein[26] and associates at the University of Pittsburgh emphasize that in addition to morphological differences between rods and cones, rod and cone pigment regeneration in isolated retinas are different. Perhaps the observed effects are due to chemical differences between rod and cone photosegments. They have used the early receptor potential to show that the frog's green-rod and cone photopigments regenerate in the isolated retina whereas rhodopsin does not. It appears that photoproducts of cone pigment bleaching may decay faster than rod photoproducts. Microspectrophotometric methods will detect rod photoproducts, but in the absence of cone photoproducts, they may have decayed to a non-visible portion of the spectrum. Differences between rod and cone photoproduct chemistry may be important in understanding why some degenerative diseases, such as retinitis pigmentosa, appear to be initially selective for rods.

MACULOPATHIES

Dr. Edward Norton[27] and associates at the University of Miami continue to study macular diseases in selected groups of patients with special emphasis on diagnosis, classification, natural history, and hereditary and familial aspects. Wherever possible, histological correlations are made with the clinical observations. These investigators have contributed to the understanding of the pathophysiology of macular diseases. Among the specific diseases studied are cystoid macular edema, idiopathic central serous choroidopathy, and senile disciform macular degeneration.

Dr. John D. M. Gass[28], Bascom Palmer Eye Institute has reviewed 200 patients with macular drusen and disciform degenerative changes. He has concluded that all of these patients have familial diseases which affect the choriocapillaris and pigment epithelium. The involvement of the overlying retina is secondary. It is important to continue the study to determine whether there is evidence that any form of medical treatment alters its natural course.

Some clinicians have advocated a therapeutic approach to the problem of central serous choroidopathy and have employed photocoagulators. Dr. Ephraim Friedman[29] and associates at Boston University Medical Center are among those who have emphasized the need for controlled studies of "nontreatment". These

investigators have presented clinical data from 27 patients with documented central serous choroidopathy who were not photocoagulated and whose condition was followed by fluorescein angiography. These investigators believe that in most cases the disease is benign and self-limiting, and therefore, may require no treatment by photocoagulation. They do recognize that in some cases photocoagulation may shorten the duration of a given episode of central serous choroidopathy; however, there are potential hazards in the treatment.

Dr. Samuel V. Vainisi[30] and associates at the University of Illinois have been concerned with the establishment of a breeding colony of babcons with heredomacular degeneration. They have been interested in the inbred colony of sixty baboons at the Brookfield Zoo. These animals are being examined, and behavioral, photographic, electroretinographic and fluorescein studies will be conducted in order to describe progressive lesions which might be detected in the macular region. These investigators observed behavioral abnormalities in a baboon which led them to suspect that the animal had visual acuity deficiencies. Clinical tests indicated that the animal had juvenile macular degeneration. It was planned that the animal would be useful in establishment of a breeding colony, however, she died of unknown causes. Histopathologic analysis confirmed the clinical diagnosis. It is assumed that the lesion may be inherited and indicates that the baboon may provide a nonhuman primate model for investigation of macular degeneration.

Further studies which involve the creation of experimental models in rhesus monkey in order to study various pathogenic mechanisms of macular degeneration are being conducted by Dr. Mark O. M. Tso[31] and associates at the Armed Forces Institute of Pathology. These investigators believe that one of the possible pathogenic factors of macular degeneration is chronic exposure to an excessive amount of light. They produced an experimental model in several stages of development by exposure of the macular region to the light of an indirect ophthalmoscope. The light provides a mild photic insult. Fluorescein angiography showed that leakage of fluorescein is the first clinical sign of damage to the macula. The leakage started 24 to 48 hours after exposure and is probably caused by a mechanism other than photocoagulation. These experiments demonstrate that a good experimental model can be produced.

TUMORS

Biochemical Developments

Retinoblastoma resembles other tumors such as lymphoma for which there is evidence which suggests a viral cause. Although direct evidence for the role of a virus is lacking, Dr. Daniel M. Albert[32] and associates at Yale University School of Medicine argue for a viral etiology in retinoblastoma. Electron microscopic examination and immunologic methods have yielded little evidence of viral infection. Based on biochemical methods, these investigators have been studying the RNA-directed DNA-polymerase activity in human ocular tumors. This enzyme is important because of its presence in animal RNA oncogenic viruses which have been analyzed. This enzyme activity has not been deminstrated in normal, rapidly dividing tissues but has been found to be present in ten specimens of retinoblastoma.

Ultrasonic Developments

At Case Western Reserve University, engineering and ophthalmic skills have been combined under the direction of Dr. Adam Boozilis[33] and Dr. Edward W. Purnell. These investigators have developed a hand held B-scan ultrasonic pulse-echo apparatus for the two-dimensional visualization of ocular tissue. The scan mechanism and display unit are sufficiently portable so that they can be rolled to the patient's bedside or into the operating room. The use of this portable unit in the operating room is the first application of B-scanning techniques in surgery. The B-scan ultrasonographic method is especially helpful in explorations of tissues behind the eye globe. A complete examination is made possible because the flexible hand held device retains the capability of larger scanners to differentiate finer tissue details.

Further work on improving capabilities of ultrasonic diagnostic systems to ensure a more reliable diagnosis of ocular and orbital tumors is being conducted through the collaborative efforts of Dr. D. Jackson Coleman[34] and Dr. Frederick L. Lizzi at Columbia University and Riverside Research Institute in New York City. A large number of patients have been examined ultrasonically, and clinical studies have demonstrated the value of B-scan ultrasonic methods for patient evaluation. These investigators have designed a dual beam scanning system. The equipment being developed by this group will enhance tissue reflectance levels and separate tissue planes, both of which are useful in demonstrating variations in ocular rumor patterns and vitreous hemorrhage. The ultrasonic measurement of tissue characteristics is being studied in order to improve the diagnostic usefulness of these methods.

UVEITIS

Studies in progress in experimental animals indicate that prostaglandins are important in the development of inflammation in the human eye. As a response to mechanical trauma or induced uveitis, prostaglandin-like substances are released into the aqueous humor. Substances with prostaglandin-like activity are not detected in uninflamed eyes. Dr. Kenneth E. Eakins[35] and associates at Columbia University have been exploring the role of prostaglandins in the physiology and pathology of the anterior uvea. These investigators have used the rabbit to demonstrate that fluorescein-iris angiography techniques are useful for recording alterations in the diameter and permeability of the uveal blood vessels. Topical application of prostaglandins produces vasodilation and an increase in permeability of blood vessels at the base of the iris which are more sensitive to the actions of the prostaglandins. The vascular alterations produced by prostaglandins in the anterior uvea may be diminished by prostaglandin antagonists. The action of prostaglandin-blocking agents may be of value in the control of the clinical condition of acute anterior uveitis.

Dr. Laszlo Z. Bito[36] and associates at Columbia University have been investigating the mechanism and characteristics of the prostaglandin transport system. It appears that a single episode of uveitis is capable of damaging an absorptive prostaglandin transport and its accumulation in the anterior chamber. The evidence suggests that there is substantial removal of prostaglandins from the aqueous humor in the posterior chamber by the ciliary

processes. Since prostaglandins are associated with [illegible] the symptoms of uveitis, the accumulation of prostaglandins may be of clinical significance.

Since the iris may modify the [illegible] of ocular tumors, the permeability of the iris capillary network is [illegible]. Dr. Ashton [illegible] and associates at the Albany Medical College have been investigating the normal ultrastructure of the iris capillaries and their permeability to tracers to establish the anatomic location of [illegible] and studied [illegible] Electron-dense, low molecular weight [illegible] were found [illegible] from ciliary capillaries and fill the extracellular space of the stroma of ciliary epithelium. Tight junctions are evident in the non-pigmented ciliary epithelium and may be the blood-aqueous barrier to low molecular weight substances. Peroxidase does enter the posterior chamber [illegible] and the transport through the non-pigmented epithelium is predominantly or [illegible] by pinocytotic activity. Transport of water and of smaller molecules may occur by mechanisms not explained by these studies. Therefore, it has been shown that the free movement of solutes between portions of the extracellular fluid in the eye is controlled by the presence of anatomic and physiologic permeability barriers. Vascular leaks occur in a variety of clinical conditions such as central serous retinopathy, macular degeneration, diabetic retinopathy as well as uveitis. Production of a satisfactory experimental model for vascular leakage will permit studies of these conditions and enhance the understanding and treatment of these clinical entities.

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CORNEAL DISEASES

The cornea is composed of three main layers. The outermost consists of typical stratified epithelium; the middle, central portion or stroma, consists of a connective tissue, consisting of collagen fibers embedded in mucopolysaccharides. The third or inner membrane, called the endothelium, consists of one layer of flat cells bathed by the aqueous humor. Accumulation of water occurs in the stroma, while the outer epithelium or the inner endothelium provides the metabolic activities necessary to maintain the dehydrated cornea. The site of the transport process, as well as the mechanism by which water is removed normally from the stroma, are of critical importance for the understanding of corneal physiology. It is now established that a fluid pump which is concerned with the maintenance of the hydration of the stroma is located in the cornea endothelium. The mechanism driving this pump and how this pump operates are not understood. Dr. Jorge Fischbarg, Columbia University[1] has, however, recently discovered that the endothelium layer generates a small electric potential. Electrical potential across biological membranes are usually associated with active transport ions. This could form the basis for the water pump which is present in the endothelium. In support of this idea, Dr. Fischbarg has noted that several drugs which inhibit the fluid pump of the cornea also depress electrical potential. The electrical potential developed by the endothelium of the cornea has also been measured by Dr. David M. Maurice, Stanford University[2]. The magnitude and size of the pump according to Dr. Maurice suggests that it could be related to the active transport of ions.

The cornea is the only tissue with high collagen content that is transparent. The collagenous material of the stroma is made up of small fibrils which occupy about 1/10 of the total thickness of the cornea. The transparency of the stroma of the cornea was first explained as an interference effect based on the perfect regularity of the collagen fibrils--the lattice theory. According to this theory, the cornea is transparent because there is a "destructive"interference of the light scattered by the individual fibers.

Recent work by Dr. George B. Benedek has discounted the need for perfect regularity in the collagen fibers in order for the interference mechanism to succeed and has indicated that the cornea is transparent because the size of the fibrils and the spaces between them are of such values that the incident visible light is not scattered. The findings of electron microscopy substantiate this view, but the effects of fixation and embedment on the regularity of the fibrils are uncertain. Clouding of the cornea was ascribed to a disorganization of the fibril lattice and Benedek considered it a result of the formation of open spaces in the structure, the so-called lakes.

This question was partially solved by measurement of the angular and spectral distribution of the scattered light by Dr. Frederick A. Bettelheim[3] at Adelphi University. Dr. Bettelheim found that the light scattered in normal bovine and human cornea is largely due to the birefringence*. The intrinsic birefringence is the result of non-random distribution of collagen fibrils at different loci. However, in the visual path most species have minimal birefringence areas. The distribution of equal birefringent areas of the cornea in different species account largely for the adaptive processes that the species evolves within its environment. According to Dr. Bettelheim,

*Double refraction

there is a strong interplay between the two tasks of the cornea: mechanical protection and transparency. Molecular superstructures are built to accomplish both of these tasks and therefore, the molecular organization of the periphery and center of the cornea may be different.

Herpes simplex infection of the cornea is one of the most important ocular virus disease. Its importance stems not only from the frequency of initial attacks, but also from the likelihood of its recurrence with progressive scarring and morbidity, and also from the fact that this is one of the few virus diseases that may in some cases be successfully treated with chemotherapeutic agents. In 1961, Dr. Herbert E. Kaufman at the University of Florida showed that 5-iodo-2'-deoxyuridine (IDU) was a therapeutically effective antiviral agent in the management of herpetic keratitis. Since then, several other promising antiviral nucleotides have been synthesized and evaluated for efficacy in control of herpes virus. Among these are: (1) cytosine arabinoside (Ara-C), (2) adenine arabinoside (Ara-A) and (3) trifluorothymidine.

In 1973, Dr. Kaufman[4] reported that trifluorothymidine appeared to be the most useful of currently available antivirals for topical treatment. Trifluorothymidine is virtually non-allergic, is approximately ten times as potent as IDU and is much more soluble. Most importantly, the rapidity and regularity of ulcer healing with trifluorothymidine is far superior to that of IDU.

Recurrent herpes simplex is one of the major problems in ophthalmology both in terms of morbidity, and in terms of visual disability. Present evidence indicates that once someone has an initial attack of herpes simplex the odds are approximately 25% of having another attack within two years. If there has been more than one attack of corneal herpes the odds are approximately 43% of having another attack within two years. The pathogenic mechanism of the recurrence so characteristic of herpes simplex infection is unknown. Many hypotheses have been proposed to explain what appears to be latent herpes simplex virus infection in many experimental animals.

Recently, Dr. Anthony Nesburn, Estelle Doheny Eye Foundation Laboratory[5], has found that latent herpes simplex virus can be isolated from rabbit trigeminal ganglia between episodes of recurrent ocular disease, whereas no evidence of herpes simplex virus infection was found in any other tissue tested. The concept that virus might not be latent within the cornea epithelium but might come to the cornea from exogenous sources has raised new hope that such recurrence might be preventable by drugs. Dr. Kaufman reported that the prevention of recurrent herpes simplex might be possible through the use of interferon. Interferon inducers such as Poly-IC were studied by Dr. Kaufman extensively and found to be very effective in rabbits and other rodents. In monkeys and in man, however, these interferon inducers seem to have only a minimal effect which disappears rapidly. Human interferon on the other hand, according to Dr. Kaufman, effectively prevents herpes infection in monkeys even when given as drops as seldom as twice a day. The finding that human interferon administered to monkeys protects against herpes is encouraging, and certainly justifies further attempts to define the therapeutic dose required, and the practicality of administration to man for the prevention of the herpes simplex keratitis.

In terms of applied clinical research, clearly one of the most exciting recent developments in corneal research is the therapeutic soft contact lens. The idea of covering the cornea and protecting it is not new, but the ability to protect the cornea with an optically clear dressing which is well tolerated has not been possible until the advent of the soft lens. Dr. Kaufman[6] developed and first reported the use of the soft contact lens for the treatment of corneal disease.

Recently, soft contact lenses made of hydrophilic gel have proven safe and effective for the treatment of bullous keratopathy. Bullous keratopathy is a condition in which the inside layer of the cornea, the endothelium, is damaged as a result of cataract extraction or because of degeneration caused by aging. It is estimated that of the five hundred thousand cataract extractions done a year, approximately five percent result in bullous keratopathy with swelling and clouding of the cornea, blisters on the surface which can be excruciatingly painful, and reduce vision. Soft contact lenses create a smooth optical surface, improving vision in a significant proportion of these patients. In addition, in the vast majority of such patients these lenses, by preventing the blisters from breaking in a painful way, restore comfort to patients who might otherwise be in agony. They will be helpful to patients who develop bullous keratopathy after cataract extraction, but also to those who develop this condition from degenerations due to aging and other causes.

In addition to their general availability for the treatment of bullous keratopathy, these moist, optically clear, protective lenses have proven useful in many other kinds of corneal disease. In some patients with arthritis, and in otherswho are merely aged, normal tear production becomes deficient and the eye dries and becomes scarred. Soft lenses have provided a moist protective blanket for such eyes. By protecting the surface of the cornea affected by a wide variety of other conditions, they have permitted corneal ulcers to heal. By creating a smooth surface, without rubbing off the surface tissue after injuries and other conditions which create irregularities in the corneal surface, they have prevented tissue damage while providing good vision. Good vision is present since their smooth spherical surface becomes the effective front surface of the eye.

Another exciting development stemming from basic research is the finding that the collagen fibrils of the cornea can be altered by heat so that the front of the eye changes its shape without the cornea becoming scarred. A procedure called thermokeratoplasty, developed by Dr. Antonio Gassett and associates at the University of Florida[6], has been used on dozens of patients with keratoconus, a bulging forward of the front of the eye which grossly distorts vision and can even ultimately rupture. This special heat probe irons the cornea back to its normal shape and permits these patients to function again without the risks and enormous expense of corneal transplantation. This procedure has shown a high degree of effectiveness.

It has been demonstrated that the corneal shape can be changed with heat, and this offers the possibility that, with further research, nearsightedness may be effectively treated, and other kinds of optical corrections may be performed in a relatively simple manner.

and, although recognized as a major public health problem, limited financial resources and other pressing medical problems often restrict the scope of trachoma control programs where they are most needed.

Although there are only six trachoma laboratories in the world today, three are located in the United States: The University of Washington, the University of California in San Francisco, Harvard. Recently a large trachoma research unit at the Lister Institute in London ceased operations after fifteen years of significant research in the field.

While trachoma is not an important public health problem for industrialized nations, only countries like the United States have the resources to sustain research in trachoma on a sufficient scale. Research aimed at controlling blindness due to trachoma can be justified on humanitarian grounds alone, but there is also a long-term economic benefit since developing countries can become self-sufficient sooner and will need less economic aid if the burden of caring for those who are economically blind is decreased while the number of productive adults is increased.

A substantial number of trachoma cases in American Indians have been reported. Since 1965 Dr. Chandler Dawson and associates[12,13], at the University of California San Francisco have been conducting controlled chemotherapy trials of trachoma among American Indians. The goals of Dr. Dawson are to evaluate the role of long acting tetracyclines in the therapy of trachoma, the role of type-specific-chlamydial antibodies in tears and serum of infected persons and to determine the effect of lysozyme on extracellular chlamydia. The results of these studies provide guidance for the Indian Health Service (USPHS) and Navajo Tribal Council in implementation of trachoma control programs.

Ophthalmologists are accustomed to identifying signs of fully expressed inherited diseases in the eye, for example, the macular cherry-red spot of Tay-Sachs disease and cornea verticillata of Fabry's disease. Physical signs of the carrier state of inborn errors of metabolism are much less frequently observed, and have never been described in some disorders. Accurate, safe, expeditious, and inexpensive tests that will identify heterozygous carriers are indispensable for genetic counseling.

Recently, such tests have been developed for Tay-Sachs disease and Fabry's disease. Dr. Edward Cotlier, University of Illinois Eye and Ear Infirmary[14], has shown that the specific enzyme deficiency that characterizes Tay-Sachs disease can be detected in human tears. Affected homozygous children show a virtual absence of the normal enzyme hexosaminidase-A, whereas asymptomatic carrier heterozygous individuals have an enzyme level that is intermediate between that of disease and normal individuals. Similar results have recently been detected for the enzyme deficiency of Fabry's disease by Dr. Cotlier and his associates[15]. Virtually no activity of the responsible enzyme, alpha-galactosidase-A was detected in the tears of affected male patients, whereas carrier female patients have intermediate reduction in activity as compared with normal individuals.

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CATARACT

One aim of lens research is to elucidate the mechanisms which result in loss of normal lens transparency. A prerequisite for this, however, is an understanding of the basis for the quite remarkable transparency of the normal lens. This transparency depends upon the maintenance of a high degree of order in the protein [illegible] molecules of the lens. Until recently, no clear evidence existed to [illegible] mechanism was responsible for this orderly configuration [illegible].

Dr. Fred [illegible] Bettelheim, Adelphi University[1], has developed special [illegible] biophysical methods that are useful for providing information on two facets of lens and cornea research: transparency and supermolecular [illegible] structure. Actually, the two facets are complementary because the [illegible] properties provide information from which one can infer what processes may lead to structural changes that cause cataracts.

Dr. [illegible] found that in the bovine lens (and later in the human lens) light [illegible] scattered only at low angles and was due to density fluctuations [illegible]. In osmotic experiments during which the lens was under aerial [illegible] frequencies, he found that the structural changes in the fiber cell cycle are quite different in the cortical and nuclear regions. From these findings, one may infer that cortical cataracts are of a different nature (coagulation of lakes and separation of fiber cells) than those in the nucleus (which include senile cataracts characterized by increasing size of aggregates of macromolecules in the fiber cell.

The behavior of alpha-crystallin protein in the lens and the mechanism by which it is converted to albuminoid and subsequently to the opaque material in cataract have long been of interest to many investigators.

Dr. Bettelheim's[2] work on the existence and function of phosphopeptides in the aggregation of alpha-crystallin appears to provide a breakthrough in the cataract field. He was the first to prepare an alpha-crystallin which gave evidence of crystallinity by X-ray diffraction. This was lost by the protein during dialysis, although the two phosphopeptides retained an altered X-ray diffraction pattern. The amorphous protein could then be recombined with the phosphopeptides to yield the original crystallin complex. The importance of this work derives from the revelation of a new and unexpected factor in the control of alpha-crystallin organization on the macromolecular level. Until Dr. Bettelheim's paper appeared, it was tacitly assumed that the alpha-crystallin molecule carried within it the machinery needed to control its configuration. Although recent work by others has indicated a possible role for sugar alcohols, sugars, and calcium ions in alpha-crystallin aggregation, that work on phosphopeptides views the problem from a fresh viewpoint.

There are many possible mechanisms of lens opacification, including those changes capable of increasing the scattering or absorption of light. The theory of light scattering indicates that aggregation of the crystalline proteins in the lens can produce opacity as in the case of cataract.

Dr. Judith Jedziniak and associates of the Massachusetts Institute of Technology[3], have provided evidence which implicates calcium in the aggregation of alpha-crystallin of human lenses. The process is irreversible and produces molecules of a size which can affect light transmission. The authors equated calcium ion and total calcium in their discussions of cataractous and aging lenses and were able to demonstrate an effect of calcium which may have some pertinence to human cataract formation. They also found important evidence of compositional changes in the higher molecular weight alpha-crystallin aggregates. During aggregation there is an increase in leucine, which would depress solubility by making the molecule more hydrophobic, and a decrease in tyrosine, possibly because tyrosine is tied up in covalent linages peculiar to the aggregation process.

Dr. Abraham Spector, Columbia University[4], has continued his studies of the effect of aging on protein synthesis and protein structure of the lens and has attempted to correlate his findings with the development of geriatric cataract. He has demonstrated that the alpha-crystallin macromolecule of the lens increases in size as a function of aging. The only chemical difference noted between the large macromolecule and normal sized alpha-crystallin is the presence of 2-3% sugar and a decrease in solubility. This finding suggests that the insolubility of the alpha-crystallin as a function of aging may be associated with the development of geriatric cataracts.

Disordered carbohydrate metabolism has been long considered a potential cause of cataract formation. In 1957 it was found that an enzyme, hexokinase, has a key role in lens glycolysis. Since the action of hexokinase on glucose is the major controlling step in lens energy metabolism, the characterization of this enzyme is of great importance. A failure of the enzyme activity, for instance, can produce a significant metabolic stress on the lens. Dr. Leo Chylack, Massachusetts Eye and Ear Infirmary[5], has studied the hexokinase and found that it consists of two forms, only one of which is prominent in the human lens. The two forms of the enzyme (or isozymes) have a different distribution in the lens and different sensitivity to the glucose concentration. The potential significance of Dr. Chylack's finding is that for the first time there appears to be a chance of correlating changes in a major enzyme during the pre-cataractous stage with the subsequent development of cataract.

The lens contains the highest concentration of protein and glutathione of any tissue of the body. This unusual characteristic imposes a need for the continuous supply of amino acid for the synthesis of these compounds. Because of its avascularity the lens must derive most of the constituents required for metabolic energy and synthetic reactions from the surrounding intraocular fluids. Although the mechanism for synthesis of amino acids appears to be present in the lens, studies from Dr. Venkat Reddy, Oakland University[6], have revealed that transport mechanisms rather than synthetic processes play a major role in supplying amino acids to the lens.

Another aspect of lens enzymes and metabolism has been studied in the past year by Drs. William Rathbun and Katheryn Wicker, University of Minnesota Medical School[7]. Dr. Rathbun has successfully demonstrated the activity of the

enzyme γ-glutamyl transpeptidase in the lens, a key enzyme in glutathione metabolism. The function of glutathione in the lens and the details of its metabolism have long been mysterious processes because of the extremely high concentration of glutathione in all normal lenses and its loss in most cataracts without leaving a trace of catabolic products. The particular mode of glutathione metabolism is of timely interest in view of the fact that it has been found recently to be involved in amino acid transport in the kidney. If it so functions in the lens, Dr. Rathbun's findings would be highly pertinent since amino acids are so important in lens metabolism.

Dr. Kenshi Satoh and associates from the Juntendo University, Tokyo, Japan[8], have restudied the fluorescence of the human lens and obtained definitive results. There are two fluorescence bands: the purple (440 nm) band is excited at 290 nm (in the long wave ultraviolet); the blue (470 nm) band is excited at 340 nm. The purple fluorescence is the major one in all protein fractions and its intensity is relatively constant with age. The blue fluorescence increases with age especially in the insoluble protein fraction. Although the application of this research to cataractogenesis is not yet apparent, there is much earlier work concerned with lens fluorescence as a diagnostic or predictive tool. More recent research is concerned with changes in certain amino acids which are correlated with the formation of dark nuclear cataract and changes in state of these amino acids (most importantly tyrosine and tryptophan). An important finding is that both these types of fluorescence are also found in the rabbit lens which is far removed from the human lens in many parameters. Thus it will be possible to carry out some experimental studies in an animal model.

The idea that exposure to sunlight may play a role in the formation of a type of cataract called brunescent cataract is at this time and is based chiefly on clinical evidence concerning the geographical distribution of such cataracts. Experimental evidence for this concept has been lacking until the recent work of Drs. Seymour Zigman, Joanne Schultz, and Teresa Yolt at the University of Rochester[9] who were able to demonstrate biochemical changes in the lenses of mice exposed chronically to long wave ultraviolet light, the only kind of ultraviolet which reaches the lens in vivo. After 11 weeks of light exposure, the mouse lenses began to show alterations in the protein fraction profile including particularly an increase in insoluble protein. Changes in permeability to amino acids and in their rate of incorporation into protein were likewise shown for dogfish lenses exposed in vitro to long wave ultraviolet light for 24 hours.

A search for early changes in the lens of cataractogenic agents has been pursued by Dr. John Kuck, Emory University[10]. Work is in progress to explore in experimental animals the combined effect of photosensitizing agents such as trimethylpsoralen and ultraviolet light and other potential cataractogenic agents like certain drugs and toxicants in food. One of the principal aims of Dr. Kuck's investigation is to determine if such cataractogenic processes are accompanied by permeability changes which can be monitored by tracer uptake before visible lesions become evident.

Dr. Robert [illegible] pigment bound to the [illegible] Dr. Cowgill demonstrated that the [illegible] pigment formed in other parts of the [illegible] bityrosin associated with the [illegible] Although the origin of the [illegible] possibility that it originates [illegible] probably arises from [illegible] condensed state to permit [illegible]

The morphogenetic properties of [illegible] Dr. Johan Zwaan, Children's Hospital [illegible] techniques, he found that crystallins [illegible] production begins at a relatively late stage [illegible] crystallin is the first protein to be synthesized in the lens [illegible] beta-crystallin. Dr. Zwaan's work also [illegible] involved in the differentiation of the lens and of the [illegible] may disturb normal development. These findings are [illegible] of congenital cataract.

Wound healing is a fundamental property [illegible] maintenance of the normal function of an organism. The process of tissue repair encompasses some of the most fundamental [illegible] the control of cellular multiplication, cell migration, and differentiation. In addition to the repair process itself, other stimuli [illegible] trigger mechanisms of mitosis can be differentiated [illegible] usually returns to normal upon removal of the stimulus. [illegible] to examine the mechanism [illegible] Dr. John Fedder [illegible] chemical and morphological events that precede all [illegible] cell division and migration in the lens. It [illegible] be induced in vitro in the central lens epithelium [illegible]

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[illegible] is a disease [illegible] characterized initially by an abnormal elevation of the intraocular pressure. This is often followed by progressive loss of vision [illegible] and eventually by total blindness. As a leading cause [illegible] it represents one out of every eight cases of new blindness [illegible] estimated that one out of every 200 Americans over forty years of age has glaucoma. [illegible] accompanies systemic disease, such as diabetes [illegible] certain inflammatory conditions.

Studies of glaucoma may be divided into three categories: (a) those which aim to elucidate the mechanism by which intraocular pressure becomes elevated, (b) those aimed at understanding the mechanisms by which elevated intraocular pressure exerts its damaging effects upon the eye, and (c) those aimed at the improvement of diagnostic methodology and treatment procedures. The goal of much of this research is to acquire knowledge which will lead to the eventual prevention of glaucoma.

Aqueous humor, the fluid which fills the anterior segment of the eye, maintains the intraocular pressure. The fluid is produced in the ciliary body where it enters the posterior chamber, passes to the anterior chamber, and is drained primarily via the trabecular meshwork, where it enters Schlemm's canal or its way to the venous circulation. In angle-closure glaucoma, the aqueous outflow route is compromised by apposition of the iris with the openings in the trabecular meshwork (the angle of the anterior chamber is closed). In primary open-angle glaucoma, the most prevalent form of the disease, the defect which leads to the abnormal increase in intraocular pressure is not as readily apparent. The central issues in much of the research on glaucoma are the determination of those mechanisms involved in the production of aqueous humor inflow and the determination of the normative and pathologic factors involved in regulating outflow.

A second aspect of glaucoma is the damage that excessively high intraocular pressure causes in the form of optic disc cupping, optic nerve fiber loss, and the resultant visual field loss. The nerve fibers atrophy in the disc, retina, and optic nerve. In addition, there is loss of the supporting astroglia in the optic nerve. It is usually assumed that the primary site of damage to the nerve fibers is at the optic nerve head, and that the loss of nerve fibers along the rest of the pathway occurs secondarily.

In addition to this research into etiology, and with finding possible means of prevention, research in glaucoma is also directed at improving diagnosis and treatment. Methods are currently being developed to allow for more accurate measurement of intraocular pressure, aqueous production rate, facility of outflow, and extent of damage to the optic vasculature, the optic disc, and the optic nerve. In addition, advances are being made in the development of improved pharmacologic and surgical treatment of glaucomatous disorders.

AQUEOUS HUMOR DYNAMICS

It is well established that a relationship between rate of

aqueous humor flow and resistance to its exit from the eye which establishes intraocular pressure at a certain level above the pressure of the intra- and extra-ocular vessels. NEI supported investigators throughout the United States and in Sweden have been examining the dynamics of this system.

Aqueous Production

Dr. Richard Brubaker and his associates at the Mayo Foundation[1] have examined the filtration coefficient of the intraocular vasculature in monkeys. They conclude from their findings that differences in intraocular pressure between individuals, the therapeutic effects of hyperosmotic agents, and the diagnostically recognized effects of water drinking on intraocular pressure are all mediated by physio-chemical events at the intraocular blood-vessel wall. The role of neural factors in this process has also been demonstrated by Dr. Bernard Becker and associates at Washington University in St. Louis[2] when they found that the instillation of hypo-osmotic agents into the third ventricle of the rabbit brain (near the hypothalamus) resulted in an elevation of intraocular pressure. This elevation of intraocular pressure was not observed in single eyes which underwent optic nerve transection but remained in the contralateral nontransected eye.

Dr. Keith Green and associates at Johns Hopkins University[3,4] have developed a mathematical model which describes and measures the various factors involved in the production of aqueous humor at the ciliary body: facility, pseudofacility, capillary pressure, active secretion, and the mean pressure index for filtration. The model has been employed in examining the long-held view that active secretory processes are primary in aqueous humor formation and that passive, pressure-dependent factors (ultrafiltration) play only a minor role. Their analysis of perfusion data from the isolated rabbit ciliary body, from rabbits in vivo, and from man indicated that the reverse obtains: that ultrafiltration accounts for approximately 65% of aqueous production. However, the situation is still not clear, because researchers at Uppsala University have presented data to the contrary. Dr. Anders Bill[6] demonstrated that increasing the blood flow in the anterior uvea and ciliary process in monkeys does not yield automatic increases in the rate of aqueous humor formation. He concluded that in the monkey, at least, ultrafiltration does not play an important role in aqueous humor formation.

In many instances, the treatment of glaucoma involves the use of pharmacological agents which reduce aqueous production. Primary among these are adrenergic substances, for example, epinephrine and carbonic anhydrase inhibitors, for example, acetazolamide (Diamox). Although the clinical value of these agents has been recognized for many years, the biochemical mechanisms by which they lower intraocular pressure are just being determined. In many tissues adrenergic agents activate adenyl cyclase to produce adenosine 3', 5' -monophosphate (cyclic-AMP). It is this "messenger" which actually mediates the physiological events which catecholamines initiate. Evidence has been reported in the past, by Dr. Marvin Sears at Yale University, that cyclic-AMP may play a central role in mediating the action of catecholamines on aqueous humor dynamics. Specifically, adrenergic agents, which decrease intraocular pressure when administered topically to the rabbit eye, also increase the concentration of cyclic-AMP in the aqueous humor. In addition, intracameral

injection of cyclic-AMP lowers the intraocular pressure. Further research along these lines by Dr. Maurice Langham and his associates at Johns Hopkins University appears to demonstrate that the relationships between epinephrine, cyclic-AMP, intraocular pressure are predominantly dependent on the alpha-agonistic properties of epinephrine[7,8].

It has been demonstrated by Dr. Monte Holland and associates at Tulane University that aqueous production is decreased and outflow facility is increased following chemical sympathectomy with 6-hydroxydopamine (6-HD) applied topically to the eyes of animals. Most importantly, they found that the beneficial pressure-lowering effects of epinephrine can be enhanced following this chemical sympathectomy. It has more recently been demonstrated by Dr. Albert Zeller at Northwestern University[9] that monoamine oxidase inhibitors have similar potentiating effects on the action of epinephrine on the rate of aqueous production and on intraocular pressure in rabbits. These findings suggested that patients with glaucoma might be aided by combining 6-HD with topical epinephrine therapy. Dr. Monte Holland and his associates conducted a series of clinical studies using this pharmacological procedure on patients suffering from glaucomas that did not respond well to standard pharmacological treatment. In one study[10] they examined epinephrine dose-response relationships and demonstrated that the chemical sympathectomy was effective in lowering intraocular pressure over a 5-decade range of epinephrine concentrations. The results of a second study[11] showed that the supersensitizing effects of 6-HD obtain with a number of alpha- and beta-adrenergic amines without systemic side effects. However, epinephrine was found to be the most desirable agent because it was effective for a longer duration. In reviewing their experiences over two years with 92 patients (128 eyes), Holland and his associates[12] concluded that 6-HD chemical sympathectomy is an adjunct for therapy which can provide a patient who has uncontrollable glaucoma a medical alternative to surgery.

Researchers at the University of Alabama, Washington University, and Uppsala University have been examining the role of steroids in glaucoma. It has recently been reconfirmed by Dr. Ralph Levene and his associates[13] that steroid glaucoma can be consistently produced in rabbits by topical treatment with a 1% dexamethasone solution over a period of a few weeks. Examination of steroid effects in humans provided even more exciting results[14] when it was found that 85 patients with primary open-angle glaucoma had significantly higher plasma cortisol levels following orally administered dexamethasone than did 77 normals. In addition, the data on plasma cortisol level indicated a possible trend with age for the glaucoma patients but not for the normals. It has also been demonstrated by Dr. Bernard Becker and his associates at Washington University that patients with primary open-angle glaucoma are more sensitive to steroids in both ocular and non-ocular systems[15,16]. Clearly a systemic endocrine marker provides the potential for differentiating individuals with glaucoma.

Differential responding to steroids might also provide a methodology for identifying individuals who may be predisposed to elevated intraocular pressure and glaucoma[17,18]. Dr. Becker and his associates have defined three groups of normal individuals in terms of their response to adreno-cortical steroids--high, moderate, and low responders. This response can be blocked to

different degrees in each of the three groups by pre-treatment with a cortisol antagonist. It was found that "blocking" occurs earlier in glaucoma patients and in high-cortisol responders than in subjects who are low or moderate responders. These data are interpreted as providing further evidence for the theory that genetic factors relate the response to steroids and glaucoma.

Research at Johns Hopkins University, Washington University, and the Medical College of Georgia has demonstrated that intraocular pressure can also be affected by the administration of a number of autacoids (hormones) including prostaglandins (PG). The prostaglandins are a group of fatty acids which are known to antagonize the lypolysis induced by adrenergic agents. Their biochemical effects are exerted on adenyl cyclase (the target of epinephrine and a number of hormones) and on an enzyme involved in the production of cyclic-AMP.

Dr. Keith Green at Johns Hopkins[19], employing the isolated rabbit ciliary-body preparation, presented data to indicate that PG enhances the permeability of the ciliary membrane which in turn results in elevated intraocular pressure. The primary site of action appears to be on the filtrative channels of the ciliary body. Dr. Tzu Chiang at the Medical College of Georgia[20] also demonstrated an increase in intraocular pressure with PG's in anesthetized rabbits and, in addition, showed that other autacoids, in contrast, caused a lowering of pressure. He also reported that plasma PG-E1 levels in patients with open-angle or narrow-angle glaucoma were found to be higher than in non-glaucoma patients.

The ocular hypertension responses to some PG's, can be antagonized by a number of agents. Dr. Chiang demonstrated this to be the case in rabbits that were pretreated with either epinephrine or progesterone[21, 22, 23]. Dr. Becker and his associates at Washington University[24, 25, 26, 27] have demonstrated that imidazole (a histaminic substance which enhances the reduction of cyclic-AMP) and indomethacin (an analgesic) were also effective in reducing the ocular pressure induced by PG's.

Dr. Keith Green[28] has also examined the effects of Δ-tetrahydrocannabinol (THC, a marihuana derivative) on aqueous humor production. THC was found to decrease the secretion and increase the filtration rate in the isolated rabbit ciliary body preparation. When live rabbits were injected with THC, intraocular pressure was found to decrease and both total outflow facility and aqueous protein level were found to increase. Dr. Green reports that the data available to date suggest that the response to THC involves vasoconstriction in the ocular blood vessels yielding a decrease in blood pressure, and thus a decrease in formation of aqueous at the ciliary body. The vasoconstriction caused by THC may also reduce intraocular pressure by increasing aqueous outflow.

Aqueous Outflow

Mechanisms involving the structures in the angle of the anterior chamber--the trabecular meshwork and Schlemm's canal--are involved in the control of aqueous humor outflow from the eye to the venous circulation. Research with

monkeys by Dr. Anders Bill and associates at Uppsala has recently show that an initial effect of constant artificial intraocular pressure elevation is a progressive increase in outflow facility[29]. However, this enhancement of outflow is only short-lived; outflow facility decreases after about two hours of maintained pressure elevation. Scanning and transmission electron microscopy indicate that the initial facility of outflow is due to damage ("punching holes") in the endothelial walls of the meshwork and of Schlemm's canal. By 24 hours, the defects are occluded by endothelial cells, blocking outflow. Along similar lines, Dr. Morton Grant and associates[30] at the Massachusetts Eye and Ear Infirmary have demonstrated that the rate of aqueous humor outflow through the trabecular meshwork and Schlemm's canal can be increased in enucleated monkey eyes by mechanically pressing the lens posteriorly. This effect was graded, reversible, and repeatable as long as the tissues in the angle of the anterior chamber were not damaged.

Employing the technique of suction gonioscopy, Dr. Bernard Becker and his associates at Washington University have examined the phenomenon of blood reflux into Schlemm's canal[31]. They found that the frequency of occurrence of blood reflux in patients is correlated with intraocular pressure level, facility of outflow, and corticosteriod responsiveness. An additional preliminary finding requiring further investigation was that the frequency of blood reflux in high cortiscosteriod responders was similar to that in glaucoma patients.

Efforts to improve the adequacy of the outflow channels make use of drugs or surgical procedures. The latter are usually reserved until all attempts at pharmacological maintenance of intraocular pressure have failed. Parasympathetic (cholinergic) agents, such as pilocarpine and anticholinesterases, are the medications primarily employed. However, employing a technique developed for the determination of small amounts of epinephrine in the presence of a large excess of other catecholamines[32], Dr. Ernst Barany and his associates at Uppsala presented evidence to indicate that epinephrine (an adrenergic) also increases outflow facility.

Advances in therapy with pilocarpine have been made using appliances that are easily placed directly on the eye. Dr. Bernard Becker and his associates have employed soft contact lenses, presoaked in pilocarpine. In a study with monkeys[33] they measured the amount of tritium-labelled pilocarpine entering the aqueous humor. It was found that there were higher and more prolonged concentrations of pilocarpine in the aqueous with this system than with pilocarpine eye drops. In a second study[34] soft-contact lens delivery of pilocarpine was examined with primary open-angle glaucoma patients who were otherwise uncontrolled on maximum medicinal therapy. It was reported that approximately half of these patients benefited from this new therapeutic technique.

The soft-contact lens technique is not without caveats. Apparently, larger doses of medication are pulsed into the eye in a relatively shorter period of time than with conventional eye-drop therapy. This raises the possibility for the occurrence of toxic effects. Another device which appears to be enjoying more stable effects employs a thin plastic wafer placed under the lower eyelid which allows a constant release of the appropriate dosage.

This device, called the "Ocusert," was [illegible] the Alza Corporation. Dr. Mansour Armaly of George Washington University[35] reports that the magnitude of the mean percent reduction in eye pressure in a group of glaucoma patients using the Ocusert for pilocarpine administration, was comparable to that with eye drops, and that the [illegible] were significantly greater.

With increasing detailed knowledge of the morphology and anatomy of the drainage system, investigators are concerned with the development of new surgical techniques. An example of such a project can be found at the Massachusetts Eye and Ear Infirmary. There, Dr. Morton Grant and his associates have attempted to devise a method of quantitative perfusion of excised segments of the angle of the anterior chamber. These experiments provide evidence that flow through this structure is very sensitive to slight physical distortions[36]. By perfusion of enucleated eyes, this research group has discovered several factors in microsurgery of Schlemm's canal that have not previously been recognized[37]. Specifically: (1) in the current surgical procedure of probe trabeculotomy ab externo there is a strong tendency for channels opened by the surgery to close again, apparently as the disrupted trabecular meshwork tissues go back into place; and (2) passing the probe inside Schlemm's canal damages the outer wall of the canal, causing changes which tend to hinder aqueous outflow through the collector channels. In addition, in comparing a number of trabeculotomy techniques in enucleated eyes, these investigators find that internal trabeculotomy yields a greater increase in aqueous outflow than does trabeculotomy ab externo and suggest, therefore, that it is more promising for clinical use.

Dr. Grant has also examined the feasibility of cyclocryotherapy in treating a number of types of advanced, inadequately controlled glaucoma[38]. At the end of follow-up periods of approximately one year, the procedure was found to have maintained a reduction in intraocular pressure in more than one half of the cases. Complications did occur in 16 percent of the cases, with significant decreases in vision in 5 percent of the patients.

Considerable research is being conducted in a number of centers to examine various types of laser surgery in the treatment of glaucoma. It is hoped that laser energy, and the concomitant benefits of laser surgery in general, can be employed in effectively decreasing intraocular pressure.

NEUROLOGICAL AND VASCULAR EFFECTS

One of the most puzzling aspects of glaucoma is how elevated pressure within the eye causes the destruction of the optic nerve. For any given level of pressure, some patients have more resistant optic nerves than others. There is considerable evidence that optic nerve destruction and the visual-field loss of glaucoma may be caused by changes in the blood circulation of the eye. Thus, it is important to evaluate the eye's circulatory system as well as the intraocular pressure in studying glaucoma.

Evidence for reduced vascularity in glaucoma comes from research at Uppsala University and at George Washington University. Dr. Anders Bill and his associates have shown that blood flow through the optic nerve head can be

improved by reducing intraocular pressure and possibly also by raising blood pressure[39]. In addition, they have also shown[40,41] that topical administration of pilocarpine and neostigmine in monkeys results in an increase in blood flow through the anterior uvea. Dr. Mansour Armaly[42] employed heat conductance as a measure of blood-flow rate in cats and monkeys. He reports that remarkable changes occur in both the choroid and optic-nerve circulation as intraocular pressure is manipulated.

Recent studies by Dr. Douglas Anderson at the Bascom Palmer Institute at the University of Miami have been concerned with the acute effects of intraocular pressure on the optic nerve. Intraocular pressure was elevated by means of a manometric system through a small needle inserted into the anterior chamber in the eyes of monkeys. Various parameters of optic disc function were studied. In one experiment[43], it was determined that the resultant ischemia produced graded effects on the optic disc which were correlated with the induced intra-ocular-pressure level. However, these were also accompanied by graded effects on the outer retina. Even though the disc and the outer retina are served by the same blood supply, the latter effect is not a common observation in glaucomatous damage. Thus, these data suggest that non-ischemic pressure-induced effects may be involved in the neuropathology associated with glaucoma. In a second experiment[44], ischemic changes in the optic nerve were studied by recording optic tract responses to flashes of light directed into the eye. It was found that elevation of intraocular pressure did not diminish nerve fiber conduction until the intraocular pressure was elevated to diastolic blood pressure. These data suggest that when intraocular pressure is elevated, the nutrition to the disc can be adequate for normal metabolic functions, and that the disc is not starved until intraocular pressure is considerably elevated.

Dr. J. Terry Ernest at the University of Chicago[45] describes a double-cannula technique for measuring, in cats, the tension of the optic disc while manipulating the perfusion pressure. His studies indicate[46] that the blood circulation at the optic disc autoregulates; that is, it can adapt to short-term decreases i perfusion pressure. This finding is supported by a study involving fluorescein angiography of the disc[47]. Dr. Ernest suggests the possibility that high intraocular pressure may contribute to the breakdown in the autoregulatory mechanism of the optic disc circulation.

A group of studies by Dr. Bernard Becker and his associates in St. Louis, [48–49] has been directed at examining drugs which may protect the retina and optic nerve from damage despite the presence of anoxia due to reduced blood circulation. These studies stem from the suggestive results of an earlier pilot study with humans in which diphenylhydantoin (DPH, an anticonvulsive) appeared to protect 1/3 of the glaucoma patients treated from field loss. Basically, employing an in vitro rabbit retina preparation, it was found that one effect of hypoxia was a reduction in the amplitude of the electroretinogram. With the administration of DPH, this reduction in amplitude was inhibited. Further studies are being conducted to examine the possible therapeutic role of DPH in greater detail.

Dr. Morton Grant at the Massachusetts Eye and Ear Infirmary[50] reports an interesting condition in which obstruction of retinal blood flow results in

elevation of intraocular pressure. He has identified and documented, in seven patients, a new clinical entity which involves a reversible unilateral shallowing of the anterior chamber, with angle closure, resulting from occlusion of the central retinal vein.

IMPROVING DIAGNOSIS

The basic tools employed in the diagnosis and measurement of glaucomatous pathology are gonioscopy, tonometry and tonography, perimetry, ophthalmoscopy, and angiography. Much current research is being directed at improving these methodologies.

Schiotz tonometry is employed to ascertain intraocular pressure by measuring the depth of indentation of the cornea when a standard weight is applied. In contrast, Goldman applanation tonometry measures intraocular pressure as the force required to flatten a standard area of cornea. Schiotz tonometry is usually performed with the patient lying down, and applanation tonometry with patient sitting. Dr. Douglas Anderson and Dr. Morton Grant[51] have compared the two techniques in 906 patients and report the following: (1) Pressure measurements with both techniques are affected by the position of the patient; (2) pressure changes with position were greater for patients under medication than for those not under treatment; and most importantly, (3) Schiotz measurements are not as accurate as applanation measurements and can be relied on for only rough estimates. In this regard, Dr. W.K. McEwen[52] has described an information-processing methodology that can be employed to improve significantly currently used data reduction techniques for Schiotz tonography. However, there are other problems with Schiotz tonometry and most current efforts (for example those by Dr. Richard Brubaker at the Mayo Foundation and Dr. Irvin Pollack at Johns Hopkins University) are being directed at improving applanation techniques[53-54].

Because one of the first signs of neural damage is excavation and cupping of the optic disc, evaluation of the disc is most important in the diagnosis and treatment of glaucoma. For example, Dr. Bernard Becker and his associates at Washington University[55] have recently measured the vertical-horizontal ratio of the optic cup in glaucomatous and normal eyes. Vertical elongation was observed in 33 percent of the glaucoma patients, but in only 4 percent of the normals. Investigations directed at improving the evaluation of the optic disc are being conducted with NEI support at a number of research centers. Among these are studies involving mathematical analyses, computer mapping, and laser and contour angiography of the optic nerve head.

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SENSORIMOTOR DISORDERS AND REHABILITATION

INTRODUCTION

When light falls on the retina of the eye, a nerve impulse is generated which passes back through a succession of structures in the brain eventually arriving at a region called the visual cortex. Curiously, the cortex is that part of the brain farthest from the eye. It is at the visual cortex that the perceived image is reconstructed from the pattern of nerve impulses arriving from the eye. In addition to constructing the visual image, the brain must also control the motion of the eyes so that the image remains located in the most sensitive portion of the retina. Further, the muscle controlling the lens shape must be activated for the maintenance of a focused image on the retina, the diameter of the pupil must be controlled for regulation of the amount of light falling on the retina, and the motion of the two eyes must be coordinated so that a single image is perceived. Most of the essential information controlling the function of the various ocular muscles is sent neither as feedback information. It represents the completion of a loop which begins with the stimulation of the retina by light.

In this program area, there are studies of disorders of this sensorimotor feedback system, such as strabismus (squint). Also found here are studies on disorders of perception, such as amblyopia. In addition to those activities which have a direct clinical impact, many studies are supported which provide more fundamental knowledge of the architecture of the visual pathways in the brain and the innervation of the muscles controlling movement of the eyes. Finally, there are studies on perception, the integrated functioning of the entire visual system to produce an image with shape, color, and three-dimensional form, an image which may be moving and which must be distinguishable against a background of many other shapes.

These fundamental studies provide essential information about the structure and functioning of the normal human visual system and thereby lay the groundwork necessary for clinical investigations into the cause and treatment of abnormal or disease conditions. Furthermore, information about the function of the visual nervous system can often be applied to questions concerning the nervous system and the neuromuscular systems of the body in general.

EYE MOVEMENT

When a person is asked to fixate, he rotates his eye causing the image of the fixation target to fall on his fovea. If he is then asked to maintain fixation on the target, his eye makes a consistent but unpredictable pattern of slow and fast miniature movements. In collaborative experiments conducted at the University of Maryland, Northeastern University, and George Washington University Medical Center, Dr. Robert Steinman, Dr. Genevieve Haddad, Dr. Alexander Skavenski, and Dr. Diane Wyman have investigated the degree to which these miniature movements are involuntary, spontaneous, or reflexive. Their results indicate that the miniature, rapid jumps of the eye (saccades) made during fixation are probably not different from the characteristics and probable function of large saccades made during visual exploration. Secondly, the investigators found that with practice both human and monkey subjects could

and nonspecific changes occur in subcellular organization. These observations in the mouse are expected to tell us much about the pathology of human extraocular muscle dystrophy.

Since all oculomotor neurons participate simply to produce a required muscle tension without regard to the type of movement, the supranuclear organization must be arranged to produce the observed motor neuron behavior. Several lines of research have shown that each of the types of eye movement (saccadic, pursuit, convergence) are governed by separate neurological substrates at higher central nervous system levels. Several laboratories have reported data indicating that inputs from these separate systems are integrated into a common neural output at or before the level of oculomotor neurons. The question is whether this integration takes place at the motor neuron itself or at some supranuclear interneuronal level. Dr. Edward Keller at the University of California, Berkeley, has studied the behavior of both the abducens and oculomotor nucleus motor neurons during accommodative convergence eye movements in the alert monkey[7]. The observed behavior was compared with that of the same neurons during versional (parallel or conjugate) eye movements. The behavior was found to be identical, indicating that oculomotor unit dishcarge is determined by fixation angle without regard to the type of movement used to reach that angle. An analysis of the unit firing rate also suggested that the separate inputs controlling vergence (antiparallel or disjunctive) and version eye movements are probably combined at some supranuclear level before the motor neuron. The present study of motor neuron response during vergence adds quantitative detail to our understanding of the final level of the oculomotor system. The results, showing that inputs from vergence and version systems are integrated at some neural level before the motor neuron, were not entirely anticipated since various studies have demonstrated the independence of disjunctive and conjugate eye movement. The vergence and version control signals seemed likely candidates for summation at the oculomotor neurons.

Dr. Alexander Skavenski and Dr. David Robinson in studies conducted at the Johns Hopkins University and School of Medicine have investigated the role of the abducens neurons in the vestibulo-ocular reflex[8]. The eye position in space is the mechanical difference between the head position in space and the eye position in the head. Head motion could disturb vision if compensatory eye movements were not generated by the brain. Head rotations produced as an animal moves in its environment lead to compensatory eye movements which prevent images from sweeping across the retina too quickly. To insure that eye position in the head is just equal and opposite to the head position in space, the brain must be able to sense head position. The resulting response is known as the vestibulo-ocular reflex. These investigators studied the motion of the eye of an experimental monkey in the light and in the dark when the head of the animal was rotated in a measurable fashion. Simultaneously, they measured the discharge rate of the abducens motor neuron. The relationship between discharge rate and eye position did not change when eye position was determined by either visual or vestibular stimulation. Further, no difference was found in the relationship between discharge rate modulation and eye velocity when the latter was induced by visual or vestibular stimulation. These results suggest that motor neuron behavior is determined only by eye position and velocity and is not determined by the type (saccade, pursuit, vergence, or vestibular) of eye movement that created the position or velocity. Changes of eye position in the

head were found to be equal and opposite to changes of the head position in space over the range of about .01 or 1.5 Hz during sinusoidal rotations of the head without vision. The investigators have suggested that there exists in the brain stem a neural integrator between the vestibular and oculomotor nuclei which converts head velocity signals to eye position signals. The phase shift observed in these experiments between the head velocity and the discharge patterns of motorneurons can be anticipated only if such a neural integrator is postulated in the path of the vestibulo-ocular reflex.

Drs. Albert Fuchs and U. Buttner of the University of Washington have been interested in the modulation of visual information processing by eye movements. During eye movements the perceived visual world seems to be stationary, whereas a moving object presented to a stationary eye causes the perception of movement. In both cases, a movement of retinal image occurs. Previous physiological studies in other laboratories have suggested that the dorsal nucleus of the lateral geniculate is the earliest station along the visual pathway where visual and eye movement interaction occurs. The investigators at the University of Washington have now studied the discharge patterns of single cells in the lateral geniculate nucleus and the pregeniculate nucleus of the alert monkey[9]. These discharge patterns were analyzed during spontaneous saccadic eye movements and unit activity was recorded either with the monkey in the dark or subjected to short flashes of light. Eye movements were carefully recorded and compared to the discharge patterns of the recorded cells. Nearly all of the units isolated in the lateral geniculate nucleus exhibited no change in activity with a saccadic eye movement in the dark or during light flash stimulation, and the investigators have concluded that no visual and oculomotor interaction occurs at the lateral geniculate nucleus. Of the 55 neurons isolated dorsal to the lateral geniculate nucleus and believed to lie largely in pregeniculate, 39 exhibited a clear change of activity with all saccades in the dark. These units either were usually silent and exhibited a burst of activity with a saccade or discharged at spontaneous rates and exhibited a pronounced inhibition with saccades. However, the activation or suppression of activity began an average of 80 milliseconds after the saccade. Of the 39 units, 26 also responded in some manner to the flash stimulus. These results indicate that the pregeniculate nucleus receives both an oculomotor and a visual input. However, the saccade-related unit discharges appear to occur too long after the movement either to participate in saccadic suppression or to aid in differentiating those movements of retinal image due to eye movement from those due to movement of the visual world, per se.

Drs. Samuel Ron and David Robinson of Johns Hopkins University have conducted a quantitative investigation of the direction and type of eye movements evoked by stimulation of each subdivision of the entire cerebellum in the alert intact monkey[10]. Each subdivision was systematically explored and eye movement and stimulus current were accurately measured and recorded. Three regions of the cerebellum were found to participate in oculomotor control. Within each region the type of eye movement was the same but the direction varied with stimulus location so that all eye movement directions were represented in each region. Saccadic movement was found to be evoked from the vermis, lobes V-VII. The directions of the saccades varied with electrode placement. Saccade amplitude was independent of pulse frequency, pulse width or pulse length, but, above threshold, increased with increasing stimulus current. Another regica

involved was the hemisphere, crus I and II and lobule [illegible], from which saccades similar to those in the vermis were evoked at [illegible] smooth movements whose velocity increased with an increase in all stimulus parameters. Smooth movements and saccades usually occurred together and usually had the same direction. The third region was the posterolateral cortex: the flocculus, nodulus, and uvula. Nystagmus (a rhythmic oscillation of the eye) was evoked from this region. All other structures of the cerebellum were considered unrelated to the oculomotor system because no eye movements could be evoked by a stimulus current of 1 milliamp. Overall, these results present a fairly coherent picture of the types of eye movements that are associated with the various cerebellar divisions. The investigators hope that these results will clear the way for more complex experiments that will provide a new understanding of the role of the cerebellum in the control of eye movements.

In studies conducted at the University of California, Berkeley, Drs. Gerald Westheimer and Sidney Blair investigated the role of the brain stem and cerebellum in the control of eye movement. They found[11] that stimulation of certain regions of the brain stem of alert monkeys caused an inhibition of saccadic eye movements. For the duration of the stimulation, no saccadic movements were carried out, regardless of the visual stimulus. However, no interference with smooth pursuit eye movements or convergence eye movements was evident, nor did accommodation or vestibular eye movements appear to be affected. These results, as have others, suggest that saccadic eye movements are different from other classes of eye movement. The function of the cerebellum in the control of eye movement was studied by Drs. Westheimer and Blair in cerebellectomized monkeys. These animals showed an inability to maintain an eccentric gaze. A saccade into the peripheral field was always followed by a drift back toward central gaze. Two other abnormalities of eye movement control were apparent: the absence of all smooth pursuit movements and, during the first week after cerebellectomy, an absence of convergence movements. This latter defect was partially overcome at longer postoperative times. However, these monkeys never fully recovered the ability to maintain a converged position of the eyes. Other types of eye movement did not appear to be affected: saccadic movement was perfectly normal, and no abnormality in any phase of the vestibulo-ocular response was observed. These investigators have suggested that there is something special about straight ahead gaze in oculomotor function since after cerebellectomy this is maintained when gaze in no other direction can be. The motor neurons from oculomotor nuclei recorded in alert cerebellectomized monkeys fired at their usual, quite rapid rates when the monkey was looking straight ahead, and their discharge rates were found to be modulated in the expected way during saccades and drifts. Thus, it appears that gaze-holding failure is not due to an inability of the motor neuron itself to continue firing. Furthermore, the results of this study argue that the mechanism for maintaining a steady impulse rate in oculomotor neurons during straight ahead gaze does not reside in the cerebellum.

In studies with Dr. Suzanne McKee[12], Dr. Westheimer has shown that smooth pursuit eye movements involve an element in their neural control that is not describable as the equivalent of a steady state eye position or a simple function of its rate of change. These findings are in conflict with Donders' Law which states that the orientation around a fixation axis is always the same no matter what movement proceeded the arrival of the eye in a given fixation

position. The data from the work of Westheimer and McKee show that Donders' Law does not hold for the pursuit system. Not only may the observed torsion associated with a moving eye differ from the torsion found during steady fixation, but the angle and the size of the torsion also varies with the direction of the motion. These investigators do not as yet have sufficient data to formulate general rules regarding the direction and extent of this additional torsion engendered by smooth eye movements. These studies, electrophysiological evidence, and subjective observations suggest that smooth eye movements, unlike saccades, are not compensated for in space perception. Apparently, significant differences exist in the neural substrates of smooth tracking and saccadic eye movements.

Dr. Barbara Gordon of the University of Oregon has studied the responses of neurons in the superior colliculus in unanesthetized cats[13]. The receptive field properties of units in the superficial layers were found to be similar to those previously described for anesthetized animals. The least sensitive portions of the receptive field, however, disappeared under anesthesia. Thus, anesthesia has the effect of decreasing the size of the activating region of the receptive field. Visual receptive fields were found in these studies to be much larger in the deep collicular layers than in the superficial layers. Some deep layer receptive fields included the entire contralateral visual field. Most deep layer units responded to a wide range of stimulus sizes and shapes, were directionally selective (responding only to movement with a horizontal component toward the periphery of the contralateral visual field), and responded maximally to rapid stimulus movement. Many deep layer units, especially those in the lateral portion of the colliculus responded to auditory or somatic stimuli. A number of units responded to both auditory and visual stimuli, and a few responded to both somatic and visual stimuli. These receptive field properties are consistent with the notion that the colliculus may be used in the control of head and eye movements made in response to moving stimuli. The cells described in Dr. Gordon's studies may provide information about how an animal is able to track a stimulus visually regardless of whether that stimulus initially impinges on its visual, auditory, or somatic sensory system.

Studies conducted by Drs. Westheimer and Blair[14] suggest that the motor pathway for accommodation (the alteration of lens shape) does not have a synapse in the ciliary ganglion while that for pupil constriction does. This conclusion comes from investigations which indicate that the sphincter iridae and the ciliary muscles of the alert monkey differ in their frequency response to intracranial electrical stimulation of the third nerve. Furthermore, local application of nicotine to the ciliary ganglion abolishes pupil constriction, but not accommodation, upon electrical stimulation of the third cranial nerve proximal to the ciliary ganglion. These results are very suggestive that there exists an uninterrupted neuronal path to the ciliary muscle. This conflicts with generally accepted theories of the pattern of innervation of the intraocular muscles.

VISUAL NERVOUS SYSTEM

Physiological studies of neuronal activity in the visual cortical area of the monkey have yielded considerable information on the functional organization of these areas. The study of area 17 has shown that at least two systems

of neurons occur, arranged in a series of columns extending from pia to white matter. One system has common receptive field properties within each column whereas the other system is aggregated according to eye dominance. A horizontal organization is also evident which corresponds to cortical layering, separating simple monocular responses in lamina IV of the cortex from complex binocular responses in several laminae. Dr. Jennifer Lund of the University of Washington School of Medicine has conducted anatomical studies designed to establish morphological correlates for these physiological findings[15].

She has attempted to determine if there is some simple basic plan of neuronal organization in the visual cortex which might correlate with and be testable by physiological studies. The monkey was chosen as the experimental animal because the primary visual cortex (area 17) of the primate is more sharply divided into a series of clearly limited laminae than is that of the cat or rat, and these divisions provide a useful set of morphological landmarks.

Dr. Lund has found three basic cell groups in area 17: pyramidal neurons, stellate neurons with spiny dendrites, and stellate neurons with spine-free or sparsely spined dendrites. These three neuron groups show different distributions in depth from pia to white matter and differ in their relationship to the zone of concentrated termination of geniculocortical axons. The neuron type most closely related to the laminae receiving a heavy geniculocortical projection is the spiny stellate cell. This cell type is restricted to lamina IV. Pyramidal neuron cell bodies are almost totally excluded from lamina IVC which contains the broadest band of geniculocortical axon projections. The apical dendrites of lower pyramidal neurons bear many fewer spines in lamina IVC than in lamina V and VI. The basal dendrites of upper pyramidal cells spread superficially and deep into lamina IVA. The area of thalamocortical fiber termination, rather than within it. Spine-free stellate neurons occur at all cortical levels and the sparsely spined varieties have not been found in lamina IV but occur in other laminae. These and subsequent anatomical studies are expected to provide us with a road map of this portion of the brain. A clear understanding of the neuronal interconnections should help to explain many of the findings of visual neurophysiologists and point the way toward further productive physiological studies of the visual process in the cortex.

The longest fibers of the optic tract reach to the upper layers of the superior colliculus of the midbrain. Dr. Gerald Schneider of the Massachusetts Institute of Technology has studied the effect of lesions of the superior colliculus in newborn hamsters on the formation of abnormal retinal projections[16]. The normal terminal area for optic tract fibers was destroyed in newborn hamsters. The animals were allowed to grow to maturity, and the distribution of the optic tract fibers was studied at that time. Considerable evidence of termination was found in areas normally devoid of such optic tract terminations: the remaining tissue of the colliculus and the thalamic nucleus. An abnormally high density of terminations was found in part of the ventral nucleus of the lateral geniculate body. These thalamic regions received connections from the superior colliculus in the normal animal. If the superficial layers of the superior colliculus were destroyed unilaterally at birth, axons from the eye contralateral to the lesion not only reached the area of early damage, but formed an abnormal decussation, crossing the tectal midline to terminate in the medial zone in the undamaged colliculus. Axons from the two eyes appeared to compete

for terminal space in this intact colliculus, because they terminated in a nonoverlapping manner. If the axons from the eye contralateral to the remaining colliculus were eliminated at birth, the anomalously recrossing axons increased in quantity and spread across the entire superior colliculus on the "wrong" side of the brain. Hamsters with such an anomaly showed wrong-direction turning in response to visual stimuli in a large part of the visual field. These studies provide new information on the factors which control the routing of afferent retinal fibers during the development of mammalian visual system. Lesions studies such as these can give important insights into the factors which control development in the normal system.

Dr. Frank Walsh of the Johns Hopkins School of Medicine and Dr. Richard Lindenberg of the Baltimore City Morgue have completed the first volume of Neuropathology of Vision: An Atlas[17]. This two volume set is intended to supplement major clinical texts by providing visual assistance to students and all physicians interested and engaged in the diagnosis of lesions involving the visual pathways: the optic nerve head, orbital optic nerve, intracranial optic nerve, chiasm, optic tract, lateral geniculate body, optic radiation, and calcarine cortex. In each case, the pathology of the structure is discussed and illustrated extensively. The authors of this atlas hope that their publication will serve to integrate basic information regarding neuroophthalmological diagnosis now found in scattered publications throughout the literature.

The retinal ganglion cell serves to integrate the responses of several retinal photoreceptors and is thus the first locus of visual image processing. Current theory holds that the output of a given ganglion cell is controlled by two spatially overlapping mechanisms: a "center" mechanism and a "surround" mechanism. For an on-center, off-surround ganglion cell, the center mechanism would cause excitation during the period when the light is on and inhibition after the stimulus is terminated. The surround mechanism would cause inhibition when the light is on and excitation after stimulus termination. The response intensity curves, which are used to describe the fields for both mechanisms, have their maximum strength in the center of the receptive field. The curve for the center mechanism has a higher mean and lower standard deviation than that for the surround mechanism.

Given these spatial and temporal characteristics of the center and surround mechanisms, it would be expected that the response pattern to a stationary stimulus would be dependent upon the stimulus location in the receptive field. According to the model, three basic response patterns should be observed for an on-center, off-surround ganglion cell: (1) in the center of the receptive field, a stationary target should produce an on-response; (2) in the distant regions of the receptive field periphery, an off-response should be observed; (3) in the region closer to the receptive field center, a double, on and off, response should be elicited.

Drs. Ray Winters, Terry Hickey, and J. Pollack, at the University of Miami, have examined the effect of variations of stimulus distance (from the receptive field center) and target intensity upon peripheral response patterns of single on-center retinal ganglion cells[18]. Their results revealed two types of on-center units. One group responded to annuli of light flashed outside the

receptive field center region with bursts of activity at both the onset and termination of the stimulus. These cells were, thus, on-center, on-off surround cells. A second group of cells gave responses that are similar to those predicted by the spatially-overlapping, dual mechanism theory: they were on-center, off-surround cells.

In related studies, Dr. Winters, together with Terry Hickey and D. Skaer, has examined the effect of varying the size of the stimulating flash of light on the responses to these two types of retinal ganglion cells[19]. The stimulating flashes were annuli of constant inside diameter but varying outside diameters. The two groups of cells could be distinguished on the basis of their responses to changes in annulus size. Regardless of the location of the stimulus in the receptive field periphery, the first group of cells showed spatial summation of both the on-excitation and off-excitation responses. The effect of stimulus size on the responses of the second group of cells was more complex, appearing to be dependent on the location of the stimulus in the receptive field periphery. If the inside portion of the annulus was near the receptive field center, in the on-off zone, then small increases in stimulus size produced an increase in the strength of the excitation whereas large changes in stimulus size led to a decrease in the strength of the on-excitation. Off-excitation, on the other hand, was a function of spatial summation across the entire receptive field periphery. Thus, the center and surround mechanisms appear to be spatially coextensive for the first group of cells but not for the second, at least in the receptive field periphery. These results add a new element of complexity to the picture of the retinal ganglion cell integrative function.

Dr. Duco Hamasaki and associates at the Bascom Palmer Eye Institute in Miami have embarked on a study of the neurophysiological impact of visual deprivation on each of the visual centers from the retina to the cortex. In a recent study[20] they have detailed the response pattern of two types of ganglion cells in the normal (nondeprived) cat retina. One type of ganglion cell exhibited the so-called sustained response: when a small stimulating target was moved to the peripheral, inhibitory, portion of the receptive field of the ganglion cell, a reduction in the firing rate of the cell was noted. Then, as the target moved from the surround to the center of the receptive field, the firing rate increased to a maximum and remained at an elevated level for the duration of the time that the target was in the center of the receptive field. The second type of ganglion cell, the transient response cell, showed no evidence of entry inhibition. However, as the stimulus reached the center of the receptive field, the firing rate increased suddenly and then dropped back to the spontaneous level almost as rapidly. The investigators have determined further that with increasing stimulus intensity, there is a linear increase in the maximum firing rate but no significant change in the size of the receptive field center. This observation indicates that the response properties of the center and surround components of the receptive field must be changing proportionately. These studies serve as the controls against which these investigators will compare data from their studies on ganglion cells from visually deprived animals.

The superior colliculus of the cat receives visual inputs from both retinae and from ipsilateral visual cortical areas[17,18,19] and the Clare-Bishop area. The cells in the most superficial collicular areas respond best to mov-

[illegible] visual stimuli, and a large proportion are selectively responsive to stimuli moving in particular directions within well-defined receptive fields. Furthermore, most cells are stimulated equally well by the two eyes despite the predominantly contralateral retinal input to each half of the colliculus. Two investigators, Drs. Barry Palmer and Alan Rosenquist, working the the laboratory of Drs. [illegible] at the University of Pennsylvania have identified those cells in the striate cortex of cats which are responsible for the cortical stimulation of the superior colliculus[21]. By stimulating these cells electrically in the reverse direction, that is, by applying electrical stimulation to various points in the superior colliculus and determining those cells in the striate cortex which responded, these investigators were able to plot the receptive fields and study the general physiological properties of these corticotectal neurons. They were found to be in layer V and were what are commonly called "complex" cells. They had large receptive fields and responded maximally to a slit or edge stimulus moving slowly across their receptive field. Most were binocular, and were direction and orientation selective. However, most of the cells identified did not show improved response summation with stimulus length when slits parallel to the receptive field axis were substituted for spots as stimuli. This is in contrast to the behavior of most other cells in the striate cortex. Also, most of these units responded very well to small moving spots as stimuli. The data from these experiments are consistent with those obtained from ablation studies in that the properties of the corticotectal cells identified are precisely those which are lost in the colliculus following removal of cortical area 17. Apparently direction selectivity and the effectiveness of the ipsilateral eye in driving collicular units are dependent on binocular, direction-selective inputs from the striate cortex.

A study of the development of visual information processing capabilities in the superior colliculus of the neonatal kitten during maturation has been conducted by Drs. Barry Stein, Elmer Labos, and Lawrence Kruger of the University of California, Los Angeles[22]. These investigators found that information processing in the superior colliculus advances with age, and a distinct maturational sequence can be demonstrated for some neuronal response characteristics. Single neurons of the superior colliculus were studied from late fetal stages up to 8 weeks of age. During the first few days of life, few active neurons were found, and those which were encountered had significantly lower rates of spontaneous activity than those found in the adult. Prior to seven days of age, visual stimuli proved ineffective although somatic and acoustic stimuli were capable of exciting some neurons in the deeper laminae. Between 7 and 9 days of age, visually responsive neurons were monocularly activated by the contralateral eye and best excited by stationary visual stimuli. Those neurons responsive to moving stimuli at this developmental stage were most effectively excited by slowly moving targets. Neurons responsive to movement only were absent. From 10 to 13 days until 7 to 8 weeks of age, the proportion of neurons binocularly activated, selectively responsive to the various parameters of movement and responsive to movement but unresponsive to stationary light, all increased progressively. Stationary light became a relatively less effective stimulus than movement in neurons responsive to both stimuli, and a tendency for neuronal fatigue with repetitive stimulation decreased. Although each property did not become apparent simultaneously, in each neuron, maturational changes in neuronal specialization paralleled the sequence of events in the development of visually guided behavior and may reflect the maturation of

the corticotectal pathway in the kitten.

The difference between the responsiveness of superior colliculus neurons to stationary light in the immature and adult cat is striking and has prompted a detailed examination of "static" properties in young kittens in order to quantify the stimulus parameters affecting response latency during critical stages of development. Drs. Stein, Labos, and Kruger[23] have now shown that the minimum as well as the range of latencies of on- and off-responses to large stationary stimuli gradually diminishes in the period from 1 to 8 weeks. By the end of this period, the latency values are comparable to those of mature animals. In these studies the off-latency displayed a wide range of change related to manipulation of stimulus variables and could be eliminated independent of the on-response by reducing stimulus intensity and duration. The investigators found that the minimum stimulus duration and intensity required to elicit a response gradually diminished during the developmental period.

In studies conducted at Harvard University, D. Van Essen and J. Kelly, working in the laboratories of Drs. David Hubel and Torsten Wiesel have provided evidence that the shapes of cells in the visual cortex of cats may correlate with their response properties to various types of visual stimuli[24]. The experimental procedure involved extracellular recording with microelectrodes from a number of cortical cells. Each time a cell was reached, its receptive field was mapped by a procedure involving the recording of its responses to spots and slits of light projected onto a screen within view of the experimental animal. After the receptive field characteristics had been determined, the microelectrode was advanced slightly to penetrate the cell. The impaled cell was then stained with Procion yellow injected through the hollow electrode. After sacrificing the animal and sectioning its brain, the investigators were able to identify the stained cells and determine their shape. Although the technical complexity of the experiment limited the number of cells mapped and stained, the results of the experiment suggest that, in the Hubel and Wiesel terminology, "simple" cells are probably stellate in shape and "complex" cells are likely to be pyramidal. "Hypercomplex" cells were identified in only two cases, and one was stellate and the other pyramidal. These studies, which provide a correlation between a functional property and the appearance of a cell, are likely to prove of fundamental importance for future studies in many parts of the nervous system.

Because of their relative simplicity and the accessibility of their neural elements, the visual systems of several crustacea have been extensively studied as models for various elements of visual information processing in mammals and man. In studies conducted in the laboratory of Dr. C.A.G. Wiersma at the California Institute of Technology, Drs. Hugo Arechiga and Keiji Yanagisawa have investigated the response to light of the visual interneurons of the crayfish[25]. These investigators have found that illumination of areas of they eye outside of the receptive field of a given interneuron results in an inhibition of the light-stimulated response of the interneuron. Regardless of the distance between the inhibitory light and the receptive field, no decrement of inhibition was found. Neither was there a tendency for inhibition to decrease with time. The threshold for eliciting inhibition from a given area upon another was much higher than the threshold for excitation of the impacted area. Dark adaptation of the eye caused a widening of receptive fields with a correspond-

ing reduction of the inhibitory area. This effect of dark adaptation on lateral inhibition is remarkably similar to that described some years ago by Horace Barlow and coworkers for the cat. In the crayfish, every field but the receptive one acts as an "off" inhibitory surround. Therefore, the change in responsiveness found by Arechiga and Yanagisawa can be attributed primarily to an expansion of the excitatory field rather than to a reduction in the inhibitory strength of the surround. This change in field organization might be neural in nature, as postulated by Barlow for the cat, or more likely, the results of a peripheral mechanism, such as pigment migration in the photoreceptive units.

Because the ground squirrel has an all cone retina, it is the experimental animal of choice when one wishes to study vision without the confusing influence of the achromatic rods. Dr. Charles Michael of Yale University School of Medicine has studied the response properties and receptive fields of opponent-color and opponent-contrast cells in the lateral geniculate nucleus of the ground squirrel[26]. The majority of the color-sensitive neurons found had the common concentric center-surround receptive fields consisting of one blue-green opponent-color system in the center and the opposite type in the periphery. That is, a given cell might respond when the center of its receptive field was stimulated by a green light but be inhibited when the same photoreceptors were stimulated with blue light; stimulation of cells in the surround elicited an exactly opposite spectral response. Because of their double opponent fields, these geniculate cells were optimally influenced by the simultaneous presentation of two different colors: one covering the field center, the other illuminating the surround. Dr. Michael also found opponent-contrast neurons with receptive fields of the same center-concentric surround arrangement. These cells had very strong antagonistic surrounds and consequently were insensitive to diffuse light. The opponent-color and opponent-contrast cells seem to be segregated into clusters in the geniculate. This investigation has speculated that the double opponent-color cells probably receive excitatory inputs from two sets of optic tract fibers with simple circular fields and with opposite types of blue-green, opponent-color properties. A single afferent fiber has a receptive field which coincides with the cell's field center. The fields of a second set of fibers are distributed in an annular fashion around the cell's center, they collectively form the surround of the cell's receptive field. An additional two groups of optic tract fibers with the opposite types of opponent-color organization and with the appropriate field positions in the center or the surround may make inhibitory synapses on the geniculate cell. The opponent-contrast cells probably receive inputs from two sets of optic tract fibers with center-surround receptive fields. A single excitatory afferent has a receptive field center which coincides with the cell's field center. The surround fibers encircle the cell's field center and collectively form the surround. They are inhibitory and probably make presynaptic contacts on the terminal of the central fiber. These studies have further shown that two general types of fibers efferent from the retina are sharply segregated. The directionally selective axons travel only to the superior colliculus while the contrast-sensitive and opponent-color sensitive units go only to the lateral geniculate nucleus. These studies have enlarged our understanding of the mechanism of chromatic stimulus integration in the visual nervous system. Dr. Michael has provided a model "wiring diagram" which may represent the general pattern in other species with color vision, including man.

Drs. Russell DeValois and Norman Morgan at the [illegible] Berkeley, together with Dr. Max Snodderly at the [illegible] Technology, have been studying the visual system [illegible] comparing their results with those obtained in human [illegible] psychophysical experiments. The rationale for the studies [illegible] experimental animal with visual system [illegible] man, on which electrophysiological studies [illegible] nervous system can be performed. In one study, the [illegible] monkey subjects was tested with [illegible] qualities. The human and macaque [illegible] in form and quite similar in absolute [illegible]. In another study, Drs. DeValois and Morgan, together with Bert [illegible], William Yund, and Elaine Hull, tested the spectral sensitivity [illegible] under scotopic and photopic conditions. The results show a striking correspondence between the species. The relative sensitivities for the two species across the spectrum were virtually identical, and the absolute sensitivities were remarkably close. These results suggest that both the spectral [illegible] of the photoreceptive pigments in the two species and the way in which different receptor responses are combined neurally are quite similar. Finally, Drs. DeValois and Richard Marrocco[29] have recorded the responses of 31 cells in the lateral geniculate nucleus of the macaque monkey. For each cell the responses to stimuli varying in wavelength and purity (spectral bandwidth) were recorded. The type of response of any given cell was determined by the stimulus wavelength. Some cells were stimulated by blue and inhibited by yellow, while others gave the reverse response. Still others represented a red-green opponent system. The response magnitude of any given cell, whether excitation or inhibition, was determined by the purity of the stimulus. The responses of these cells, taken together, are entirely consistent with the spectral sensitivities obtained for this same monkey species in the psychophysical experiments. Thus, this work contributes to our understanding of the role of these lateral geniculate cells in monkey, and perhaps human, perception of color.

Dr. Gunter Von Noorden of the Baylor College of Medicine has demonstrated[30] that unilateral lid closure of visually immature rhesus monkeys cause irreversible amblyopia in all animals so treated between birth and nine weeks of age. If the treatment is delayed until twelve weeks of age, no amblyopia appears. During the age of susceptibility, Dr. Von Noorden found that periods of occlusion as brief as 2-4 weeks were effective in causing severe amblyopia. Amblyopia also appeared in those monkeys which were made strabismic during the first week of life. Correlation of these data with those obtained from human patients indicates that the human visual system remains sensitive to unilateral lid closure (induced for therapeutic purposes) for a longer period of time than the monkey's. These results with the monkey are particularly provocative because of the similarity of the visual system in this animal to that of man. In other studies[31], this investigator has examined the histologic changes in the visual nervous system resulting from unilateral lid suturing or artificial strabismus, again in the immature rhesus monkey. Sections from the retina, lateral geniculate nuclei, and areas 17 and 18 of the visual cortex from monkeys with behaviorally demonstrated amblyopia were compared with similar tissues from normal monkeys. The only histologic change observed in the deprived monkeys was a significant reduction of cell section area in all layers of the lateral geniculate nucleus that received input from the deprived or deviant eye. These

limits of the normal ipsilateral projection. The [illegible] that while ma-
ture effects of strabismus on the primate, [illegible] the
functional significance of this has yet to be demonstrated.

If the visual experience of young cats is altered systematically, the
population of neurons in the primary visual cortex is found [illegible] examination, to be altered. The alteration can be described as a change
in the selective responsiveness of the neurons to some of the patterns of excit-
ation they have detected. To produce these [illegible] the cats are reared
[illegible] during a critical period [illegible]. These
effects on the visual cortex [illegible] to be permanent, but have so far been studied in a way that the experience that
caused them [illegible] studies conducted at the University of Wisconsin, Berkeley,
Drs. Janet Pettigrew, Alfred P. Bonds and Lars Liden have shown that single
neurons in the cat's visual cortex can be induced to increase their respon-
siveness to repeated stimuli which are applied while the neurons are under
observation[1]. These short-term changes are of the same direction as the
permanent modifications studied by Wiesel and Hubel[2] in kittens following
experimental manipulations during the critical period of normal development.
However, the changes observed in these investigations were less pronounced and
probably transient. These experiments demonstrate the facility with which
changes in the organization of the visual cortex can occur in visually
immature animals.

In studies conducted at the University of Washington, Drs. Lorraine Lund,
J.T. Cunningham, and Jennifer Lund have shown that the removal of an eye in
newborn rats results in an increase of uncrossed projections from the intact
eye to the anterior [illegible] lateral geniculate nuclei[3]. The additional
uncrossed projections arise from areas of the retina which would normally pro-
ject only contralaterally and terminate in regions of the geniculate and
colliculus which, in turn, would normally receive only crossed optic axons.
The increased ipsilateral projection does not occur if enucleation is delayed
until after the critical period[4]. These studies were stimulated by the hypothesis that
although the mammalian central nervous system has only a limited ability to
regenerate damaged elements following experimental lesions, functional recovery
of substantial portions can sometimes follow a lesion. This hypothesis sug-
gests a reorganization or reinforcement of existing pathways. In younger
brains the degree of recovery after damage appears much greater than in adults.
These investigators have interpreted their findings as an indication that at
the time of the lesion, many axons of the normal optic tract have already crossed
the optic chiasm, but others have yet to arrive. When the later-growing axons
reach this region of the aberrant animal the [illegible] factors determining that they should cross to the contralateral side are no longer present.
These axons then distribute, some contralaterally as they normally, or
they distribute all to the ipsilateral visual centers. This apparent reorgani-
zation of growth patterns is probably in contrast to the plasticity demonstrated
in the adult after eye removal. This seems to be [illegible] The result is a take-
over of postsynaptic sites vacated by degenerated optic terminals. The results
of these studies also argue that the critical period during which deprivation
or distortion of visual input permanently affects the organization of visual
centers might be a reflection of the time course of axonal outgrowth in late-
developing mammalian populations, rather than intrinsic plan for maturation

of synapses [illegible] connected. Such an hypothesis is [illegible] with [illegible] terms of plasticity.

[illegible] studies conducted at the [illegible] examined the response characteristics of neurons in the striate and prestriate cortex of normal macaque monkeys and found that [illegible] of form deprivation or strabismus. Most neurons were best activated by visual stimuli that had elongated shapes and were oriented [illegible] the receptive fields of the cells [illegible] The neuronal responses depended [illegible] In normal animals, most of the cells [illegible] In striate cortex [illegible] of the cells in the prestriate cortex only [illegible] were monocular. [illegible] the binocular cells in these [illegible] The most prevalent [illegible] In the first class were those cells that gave a binocular response almost equivalent to the monocular response from the dominant eye and [illegible] In the latter class, the binocular disparity produced little change in the response. This type of neuron was seen in both striate and prestriate cortex. [illegible] monocular cells, seen only in the prestriate cortex, the number of action potentials evoked by the stimuli depended upon retinal disparity. [illegible] of these cells the response was markedly facilitated by [illegible] disparities. Using these results from normal animals as a [illegible] investigators turned their attention to visually deprived animals which [illegible] had undergone lid closure of eye surgery to produce a [illegible] deprivation. The acuity in each eye of every animal was tested [illegible] The neurophysiological results demonstrated that the [illegible] was paralleled in terms of behavioral change. [illegible] animal with very poor acuity in the deprived or strabismic eye. The [illegible] neurophysiological correlate was the presence of [illegible] which was stimulated almost [illegible] by the normal eye. These results suggest that visual deprivation of whatever type caused a [illegible] in the architecture of the higher visual centers.

PERCEPTION

A number of studies in the laboratory have demonstrated that the main function of eye movements during fixation is the maintenance of seeing. Experimental procedures which [illegible] image in a given portion of the retina despite eye movements. When this is done, the image contrast and edges within the [illegible] target [illegible] within a few seconds. Rapid, miniature movements of the eye are [illegible] in maintaining clear visibility of a stabilized image. However, [illegible] movements over one minute of arc in magnitude and less than [illegible] to maintain the visibility of the target. Dr. Tiker Tulunay-Keesey of the [illegible] of Wisconsin has previously shown that flickering a stabilized image [illegible] thus causing a temporal change of luminance over the same retinal receptors, also [illegible] the duration [illegible] target visibility. This effect is dependent on the use of low flicker rates. In more recent [illegible] Dr. Keesey has studied the ability of human observers to see a [illegible] that was only slightly brighter than an [illegible] field. The experimental procedure involved

a variation of the ratio of target [illegible] as well as the rate of flicker frequency of the [illegible] within the frequency range used, the most effective [illegible] was the lowest one, 0.4 Hz, regardless of [illegible]. [illegible] increased. At lower frequencies, [illegible] maintaining visibility; however, at [illegible] the effectiveness of flicker was reduced, [illegible] determining the level of visibility of [illegible]. These results confirm once more that slow drifts of the image across the retina are [illegible] keeping the target continuously visible. In [illegible] Dr. Vasilievskii, Dr. Keesey has shown that photopic visual sensitivity is modulated by the movement of the eye, that is, by the movement of the image on the retina. When the image was free to move across the retina, as in normal viewing conditions, an incremental flash upon a continuous background was detected at levels of luminance which depended on the extent of the retina illuminated by the background. This is the well known desensitization-sensitization effect, described by Westheimer. Stabilization of the image of the flash and the background on the retina greatly reduced the dependence of sensitivity upon illuminated area. Dr. Keesey has speculated that retinal sensitivity is mediated by both the "sustained" and "transient" systems in normal vision and primarily by the "sustained" system when the images are stabilized on the retina.

When different images are presented to the two retinas of human subjects, the visual system strives to produce a single perceived image. This fusional response is believed to be made of two distinct components: (1) a central fusional response whose magnitude is limited to the extent of the so-called Panum's fusional areas and (2) a motor response in the form of compensatory eye movements. Dr. Andrew Kertesz of Northwestern University has reported that retinal images which differ by a rotational component are fused by a purely central mechanism without any evidence of compensatory eye movements[45]. Thus, cyclofusional stimulation appears to offer a valuable approach to the study of the central components of the fusional response, the dynamic aspects of Panum's fusional areas. The central response involves detection or assessment of the disparity and the processing of the disparity in the interest of binocular vision. Dr. Kertesz has conducted several experiments designed to explore the processing of disparate retinal images by the central fusional mechanism. In one study[46], he has developed data which suggest that the prime strategy of the central mechanism is to bring the largest possible portion of the two retinal images into correspondence. Given this portion, the visual system appears to discard the rest of the stimulus pattern as noise which is not a valid part of the stimulus. When the fusional mechanism is operating, this noise is not perceived by the subject. Dr. Kertesz suggests that two central mechanisms could be postulated to explain the visual system's approach to assessing the retinal image disparity: a mechanism that is tuned to orientational disparities, or one that serves to detect positional disparities. He has now produced data[47] to support his contention that it is the disparity (introduced by the stimulus at each pair of retinal points in the two eyes) to which the fusional mechanism primarily responds. The angle of displacement between the two images does not appear to be as important a stimulus to the visual system. These results correlate with those of other investigators who have demonstrated binocularly-driven cortical disparity detectors in the visual cortex of the monkey and cat.

Psychophysical studies on the mechanism of stereopsis conducted by Drs. Whitman Richards and David Regan at the Massachusetts Institute of Technology have raised the possibility that two separate mechanisms function for the processing of binocular cues for depth[43]. The experimental subjects were asked to fixate on a given point in space and were presented with stimuli consisting of parallel bars. The viewing system was arranged so that each eye could view only one of a pair of bars, and the two eyes were required either to converge or diverge in order to produce a single perceived image. The MIT group has found a number of subjects who are capable of processing one type of stimulus, for example convergent disparities, but not the other. When the ability to process both convergent and divergent disparities is present in the individual, the existence of two separate mechanisms can still be demonstrated by plotting field maps for stereopsis for each type of disparity. Extensive measurements on one observer have shown that the zone of the visual field over which convergent disparities are processed may differ quite distinctly from the zone over which divergent disparities can be integrated. Furthermore, Dr. Richards has found that for those individuals who possess one or the other of the stereo-processing mechanisms, a contrast reversal of the stimuli and backgrounds may lead to a reversal in apparent processing mechanisms[44]. Thus, those who are able to process convergent disparities presented as light bars on a dark background, when presented with dark bars on a light background, may lose the former inability to process divergent stimuli but now lack the ability to process convergent stimuli. Dr. Richards has suggested that such reversals in depth with contrast may be the result of interactions between the center and surround components of the disparity mechanism.

Dr. Patricia Ondercin, with Drs. Nathen Perry, Jr. and Donald Childers of the University of Florida have studied the phenomenon of ocular dominance[45]. They have found that dominance appears to be a continuous function which is normally distributed in the general population. By placing lenses of various dioptic powers in front of one or the other eye of the test subjects, the investigators were able to establish, enhance, or decrease ocular dominance by modifying the image clarity in one eye. These results indicate that dominance, as measured by dichoptic stimulation, is not a static characteristic even in adults. In these experiments dominance was shifted to the nondominant eye even in subjects showing strong ocular dominance under normal viewing conditions.

In a joint experiment conducted by Drs. Joseph Sturr and Davida Teller at Syracuse University and the University of Washington, respectively, the interaction of the two eyes was evaluated when a test stimulus was presented to one and an inhibitory stimulus to the other[46]. These studies were conceived as a further test of the physiological site of the Westheimer effect. Dr. Westheimer has shown that the threshold of perception for a small test spot located in the center of an illuminated disc varies with the diameter of that disc. The threshold for the test spot rises with increasing disc diameters, reaches a maximum for an intermediate disc diameter, and then falls again. This desensitization effect has been attributed to the existence of an antagonistic surround in the receptive fields of neural units within the retina. Concentric receptive fields are known to occur in various vertebrate species at the bipolar, ganglion, and lateral geniculate levels as well. The studies of Sturr and Teller were designed to expose the possible interactions of stimuli to the eyes of the higher centers of the visual nervous system. In their studies, the test flash

was presented to one eye and the sensitizing disc or annulus was presented to the other. With steady presentation levels, dichoptic interactions were found to be small or nonexistent. However, under transient conditions, dichoptic and monoptic effects were remarkably alike. These results are consistent with the conclusion that steady state disc annulus interactions and transient disc annulus interactions probably occur at more peripheral and more central locations in the visual nervous system, respectively.

Frank Bagrash, a student of Dr. James Thomas of the University of California, Los Angeles, has conducted a series of experiments which suggest that the human visual system contains tunable channels which can affect the transformation of the photic stimulus into a perceived image[47]. The experimental procedure involved measurement of threshold intensity for light discs of varying diameters. When the subject briefly observed an adapting disc of given diameter at suprathreshold level, his subsequent threshold of perception for a test stimulus was markedly increased when the test stimulus was of the same size as the adapting stimulus. However, when the test stimulus differed markedly in size from the adapting stimulus, no significant difference in threshold intensity was observed between control and adapted trials. In other experiments, annuli were substituted for the adapting disc. The data of these experiments suggest that adapting area is not the sole determinent of the observed effect. The spatial distribution of the adapting area and its interaction with intensity both appear to play a role. Dr. Bagrash argues that the effect of size tuning on threshold intensity can best be accounted for by some multiple, as opposed to single, channel tuning mechanism interpretation. These investigators, together with those in several other laboratories around the world, are exploring the implications of psychophysical studies which suggest that the visual nervous system "tunes in" those portions of a stimulus which are of interest and "tunes out" much of the additional visual information presented simultaneously.

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ANNUAL REPORT
NATIONAL EYE INSTITUTE
July 1, 1973 - June 30, 1974

REPORT OF THE DIRECTOR OF INTRAMURAL RESEARCH

Carl Kupfer, M.D.

Although the National Eye Institute's Intramural Program will always constitute only a modest portion of the nation's total vision research effort, its continued development is crucial, not only for direct research activities, but for the evolution of NEI's total program. The expertise centered in the Clinical Branch and Laboratory of Vision Research, as well as the Office of Biometry and Epidemiology, serve as an invaluable resource for all Institute programs, providing guidance to extramural program management, program planning and analysis, and the Office of the Director. In general, the scientific direction of the Institute is greatly dependent upon this highly-regarded corps of professionals, many of whom are internationally known for their research contributions.

In a time of decreased Federal emphasis on research training, the intramural research facilities of the NEI can also serve the young investigator who desires experience in a stimulating intellectual atmosphere, as well as the senior vision research scientist who wishes to take advantage of the unique resources and opportunities for collaboration at the National Institutes of Health.

The Eye Institute has the only eye clinic in the United States where beds are allocated solely for the purpose of vision research and where there is such close and consistent collaboration between clinical and laboratory scientists. Its progress during the short time of Dr. Ballintine's administration has been noteworthy; yet, its needs remain critical. Because of limited staff there are no studies underway in two of the Institute's five major programs: Cataract and Corneal Diseases. Other programs are only minimally represented. In the coming year, major emphasis will continue to be placed on strengthening this vital program to further its development as a national resource and model for clinical vision research.

ANNUAL REPORT
CLINICAL BRANCH
July 1, 1973 - June 30, 1974

REPORT OF THE CLINICAL DIRECTOR
Elmer J. Ballintine, M.D.

The Clinical Branch has continued to develop its program of studying ocular disease in patients by laboratory methods. Patients are admitted to the Clinical Branch only if they are appropriate for enrollment under one of the research plans. These research plans must meet the same standards of scientific validity that are imposed on non-human experiments and, at the same time, must be ethically acceptable and incorporate appropriate safeguards for the patient's rights and welfare.

During the year a six member Protocol Review Committee, three of whose members were not physicians and three not part of the staff of the Clinical Branch, began a detailed reivew of all research protocols in the Clinical Branch for scientific merit and ethical acceptability. Each investigator has revised his research plans to meet the requirements of the Committee. It is expected that additional review by Clinical Center agencies will be required in the near future.

The renovation of the outpatient service area was largely completed and we moved from our temporary quarters. The renovation of laboratories for tissue culture and for the study of retinal and choroidal biochemistry was completed. A completely renovated operating room, equipped for ocular microsurgery, vitreous surgery, and electroretinography was completed. Apparatus for performing B-scan ultrasonography of the eye and orbit was placed in operation. Equipping a laboratory for neuro-ophthalmology was also begun.

The staff of the Clinical Branch consists of four senior staff physicians, three physicians who are clinical associates, and one who is a staff associate. Two senior staff members are not physicians. Eight biologists and technicans and four secretaries support the staff. The commitment of the staff to investigate the important categories of disabling and blinding eye diseases is apparent in the individual research project reports.

In addition to conducting research on its research protocols, the Clinical Branch in collaboration with the Experimental Pathology Section of the National Eye Institute Laboratory of Vision Research, examines histopathologically approximately 100 eyes per year, most of which come from the autopsy service of the Clinical Center. Consultations were furnished for 850 patients being cared for by other Institutes in the Clinical Center. There were 2,550 outpatient visits during the year, 150 admissions to the inpatient division, and 75 operations were performed.

The Clinical Branch conducts several investigations in the field of glaucoma. One of these is the prolonged observation of a series of patients with ocular hypertension. These observations are expected to help determine which signs have value in predicting which patients will eventually require

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treatment, and to determine if early treatment of ocular hypertension has any value in preventing visual field loss.

The study protocol has been completed and registration of patients is continuing. Closely related to this project is the continuing study of the factors affecting intraocular pressure and their alteration by pharmacologic agents in young and old normal subjects and patients with ocular hypertension and glaucoma. A study of the mechanisms responsible for the patterns of intraocular pressure variation allows a clear understanding of the actions and suitability of pharmacologic agents used to treat glaucoma.

The aim of a related study which is on the enucleated, arterially perfused cat eye is to determine the pharmacodynamics of agents able to alter intraocular pressure and to further the understanding of mechanisms which maintain the intraocular pressure. A schema to explain some mechanisms by which aqueous humor is formed has been developed and the mechanisms of drug inhibition of aqueous humor formation has been clarified.

Glaucoma-related studies are underway to determine the rates at which sodium and chloride ions enter the aqueous humor and the effect of unilateral common carotid artery ligation upon the flow of blood to the ciliary body and upon the formation of aqueous. Findings have shown that there is a reduction of ciliary body plasma flow which is associated with decreased aqueous humor formation. This is consistent with the view that aqueous humor is produced by ultrafiltration. The relationship between blood flow in the ciliary body and aqueous humor formation had not previously been demonstrated in vivo. The definition of this relationship allows a better understanding of the mechanism of aqueous humor production and may be important in the management of glaucoma patients.

NEI scientists have developed an animal model suitable for studying the effects of chronic elevation of intra-ocular pressure. The researchers induced an experimental glaucoma in the eyes of normal rhesus monkeys by repeated circumferential photocoagulation of the recess of the anterior chamber angle. This technique produces a reduction in the coefficient of outflow and a chronically sustained moderate elevation of intraocular pressure similar to that seen in human chronic open angle glaucoma. Cupping of the optic nerve head, bowing of the lamina cribrosa and loss of retinal ganglion cells in the perifoveal region similar to the changes seen in human simple glaucoma accompany the elevation of intraocular pressure. This model will provide a tool for studying why and how glaucoma causes visual loss. It will allow investigations that cannot be performed in man but are necessary if we are to understand the effects of glaucoma in patients and it will permit comparisons of retinal optic nerve function in the glaucoma eyes to those in the control eyes. The effects of chronic elevation of intraocular pressure upon the rate of formation of aqueous humor will be investigated.

Other investigators have shown that blastic transformation of a patient's lymphocytes induced by phytohemagglutinin can be inhibited by gluco-corticoids. The sensitivity of this inhibition may be related to whether the patient has glaucoma or not. This effect is being systematically investigated in families of normal subjects and in glaucoma patients and their families.

Eye Institute scientists are looking for methods to demonstrate and assay a possible vasoproliferative factor in the vitreous humor of patients with such vasoproliferative diseases as diabetes mellitus, sickle cell disease, Eales' disease, and central retinal vein occlusion.

NEI scientists are also carrying out a trial of argon laser photocoagulation for patients with several diseases of the retinal and choroidal vasculature and of the macula. All patients undergo an exhaustive evaluation before treatment and during the follow-up period. It is hoped to gain considerable more clinical information about treated and untreated individuals with these diseases. Approximately 50 patients have been treated of whom 35 have diabetic retinopathy but were ineligible for the nationwide, NEI supported, Diabetic Retinopathy Collaborative Study. Two other projects are attempts to search for, properly classify, and clinically define new techniques which will elucidate the cause, prevention, or treatment of selected choroidal-retinal degenerative diseases (such as retinitis pigmentosa and familial macular degeneration), and of a broader range of genetic and familial diseases.

NEI scientists are also attempting to characterize the biochemical properties and functions of the visual pigment in vertebrate retinal receptor outer segments. Of particular interest has been the finding that rhodopsin in vitro is phosphorylated by the terminal phosphate group of ATP and that this reaction is stimulated approximately two-fold in the light. Studies are underway to determine if this reaction occurs in vivo, and if so, to quantify its extent and reversibility under various conditions of dark- and light-adaptation, and most importantly, to determine its role in the physiology of vision.

Clinical Branch scientists are studying the usefulness of radioiodinated chloroquine analog for the diagnosis and detection of intraocular melanoma. The patients included in this study are those referred to the Institute for evaluation of pigmented lesions of the eye, resembling malignant melanoma and those patients in whom the ocular media is opaque. The value of using I-125 labelled chloroquine analog for the detection of intraocular melanoma is being studied. Based upon the patients studied to date it appears that the I-125 chloroquine analog offers some aid in the differentiation of patients with intraocular melanoma from other patients with benign lesions or with metastatic disease. To date there have been no verified false positive tests, but the use of this test is not the final word in the differential diagnosis of malignant melanoma inasmuch as there have been three false negative tests to date. Another project has the broad objective of applying current procedures for psychophysical tests, improving their form and scope, and enhancing the usefulness of ophthalmic instruments for clinical work. The data generated by these instruments and methods for visual examination contribute to the other research projects within the Clinical Branch.

The results of a study designed to determine whether the Bausch and Lomb "Soflens" and the American Optical "Bandage Lens" are effective in the treatment of bullous keratopathy are being prepared for publication. Finally, there is a study designed to evaluate the efficacy and safety of n-acetyl-l-cysteine, a mucolytic agent in the treatment of the signs and symptoms of keratoconjunctivitis sicca. This investigation will provide needed information

on the treatment of patients with dry eye conditions. Evaluation of conjunctival goblet cells will allow a clearer understanding of the pathologic mechanisms involved in keratoconjunctivitis sicca.

The Clinical Branch has continued to cooperate with other Institutes in the pursuit of unique research opportunities. A cooperative effort was continued in diabetic retinopathy as part of the study of diabetes among the Pima Indians by the Epdemiology and Field Studies Branch of the National Institute of Arthritis, Metabolism, and Digestive Disease (NIAMDD). A study of microangiopathy was undertaken among the group of patients with acromegaly at the Clinical Center by NIAMDD. Other cooperative studies include: the study of immunologic aspects of ocular malignant melanomas in cooperation with the Cellular and Tumor Immunology Section, Laboratory of Cell Biology, Division of Cancer Biology and Diagnosis of the National Cancer Institute; and the study of Sjogren's syndrome among patients originally examined by the National Institute of Dental Research.

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The Laboratory of [redacted] is divided into four sections: Biochemistry, Experimental [redacted], Experimental Pathology, and Neurophysiology. During [redacted] a major activity of the section on Biochemistry was studies of the [redacted] and metabolism of the lens. The changes in carbohydrate metabolism [redacted] and water [redacted] of lens proteins, and various lens enzymes have been studied during aging and as a result of organ or tissue culture.

The major finding in this [redacted] that in the bovine lens and apparently in the human lens, a [redacted] crystallin emerges with aging. The newly emerging [redacted] in the older lens has a molecular weight of 54,000, whereas the [redacted] in the young calf lens has a molecular weight of 21,000. The [redacted] of larger molecular dimensions predominates over the lower molecular species in the older human lens, while on the contrary in the younger lens the smaller form is found in greater abundance. Apparently, with aging, as less lenticular fibers are laid down, the [redacted] that is synthesized is the one with the higher molecular weight. This age-related change in the [redacted] is one of the first examples of the effect of aging on lens proteins. This is important because an understanding of the basic chemistry and physiology of the lens is needed to understand the cataractous process.

Another major discovery was the identification of the necessary conditions to culture dissociated epithelial cells of lenses from normal and cataractous adult mice. This provides us with another means of studying cataracts, particularly congenital cataracts. Now that it is possible to take single lens epithelial cells and grow sheets of epithelium, a thorough study into the nature of the defect in cataracts should be possible. Currently this study has been extended to the congenital mouse cataract. With this organ culture procedure [redacted] scientists hope to determine the optimal conditions which will maintain the transparency of the lens for a protracted period. They are also attempting to grow isolated cells of the lens epithelium in tissue culture to determine if these cells can maintain their differentiative properties.

The purpose of another project is to study the mechanism of formation of cataracts in experimental animals and to explore possible means by which the cataracts can be prevented. Sugar cataracts can be induced in these animals by making them diabetic with streptozotocin chemical agents, or by making them galactosemic or [redacted]. Another approach to study these cataracts is to employ the lens organ culture technique. This can be done by exposing the isolated lens to elevated levels of either glucose, galactose, or xylose in the incubating medium.

The major finding of this study so far has been the continuing evidence supporting the concept that the enzyme aldose reductase is involved in initiating sugar cataracts. This enzyme seems to be the common mechanism by which the sequence of events leading to the development of diabetic, galactosemic, and xylosemic cataracts is initiated. An active inhibitor of aldose reductase (A.R.) has recently been shown to prevent cataractous changes in cultured lenses exposed to high concentrations of galactose. However, improved methods of delivery of the A.R. inhibitor by topical application must be achieved before this procedure of controlling cataract formation can be considered effective.

NEI investigators hope that this type of study on sugar cataracts may serve as a model by which other mechanisms of cataract development can be uncovered, and may also provide alternate means of preventing cataracts. Even though the initial phase of cataract development may be different in the other forms of cataract, it appears that the terminal stages are quite similar.

The aim of a third project within the Laboratory of Vision Research Section on Biochemistry is the study of factors which determine the normal development and function of the retina and pigmented epithelium. The influence of hormones on normal and abnormal development and the uptake and binding of vitamin A in the retina have been investigated during embryonic development. Biochemical analyses of enzyme activities were performed to assess the effects of hormones on the retina after in vivo application or incubation with retinas in organ culture.

Major findings of this project have been: that the hormone cortisol affects normal enzyme development in the embryonic retina while progesterone appears to retard normal biochemical development; that a specific, high affinity receptor that binds vitamin A has been found in the embryonic retina; that pigmented epithelium cells respond in culture to hormones such as thyroxine and cyclic AMP with marked changes in pigmentation, morphology, and enzyme activity. This work attempts to pinpoint early signals, such as hormones and vitamin A uptake, that are critical to normal retinal development and contrast them with those found in the diseased state. It is hoped that such studies will ultimately uncover compounds which can correct retinal development in the embryo.

The LVR, in cooperation with the Laboratory of Chemical Pharmacology of the National Heart and Lung Institute, is investigating the concentrations of cyclic nucleotides in retinal photoreceptors. These have been found to fall dramatically when a dark-adapted retina is exposed to light. These intracellular hormones may act as intermediates in translating the initial photic stimulus on the retina into the neural response which is transmitted to the brain. This project is designed to study the enzymes of cyclic nucleotide synthesis and degradation to determine the critical point at which light exerts its influence.

The major finding of this project was that extremely high concentrations of cyclic GMP were found in retinal photoreceptors. The levels of both cyclic GMP and cyclic AMP were found to be dependent on the percentage of light-bleach of the retina. Phosphodiesterase, the enzyme of cyclic nucleotide metabolism, was found to be activated by light and thus control cyclic nucleotide concentrations in the photoreceptor. This is the only well-defined enzymic activity known to be regulated by photic energy. It is hoped that this study will lead to a better understanding of the biochemical basis of the process in normal vision and lay the groundwork for an understanding of the underlying problems of retinal degeneration and blindness.

In cooperation with the Laboratory of Pathology at the National Cancer Institute, the LVR is attempting to isolate specified membrane proteins on ghosts of rabbit corneal cells derived from tissue culture and primary culture of cells from normal tissue.

Herpes simplex virus (HSV-I) - induced antigens have been demonstrated on membranes of infected rabbit corneal cells (SIRC line) by specific immunolabeling. The use of the hybrid antibody method for localization of antigenic changes on viral-infected corneal cells represents, as far as can be determined, the first application of this method of immunolabeling to experimental studies directed at control of herpes simplex keratitis.

Another project is the study of structural and functional aspects of the bovine rhodopsin molecule.

It has been postulated that hydrophobic bonding between rhodopsin and the lipids of the rod outer segment membrane is of major importance for the maintenance of the structure of the membrane and for the functional role of rhodopsin in that membrane. The thermodynamic values which have been obtained here support at least the first of these concepts, and we now have a clearer concept of the magnitude of the forces which are involved in rhodopsin-lipid interactions in the membrane. Additionally, NEI investigators now have the ability to predict molecular dimensions for various models of the structure of rhodopsin and to consider these for consistency with other evidence concerning the behavior of rhodopsin during the visual process. In furnishing information concerning the structural and functional role of rhodopsin in the rod outer segment, these studies are intended to contribute to an understanding of the basic biochemical mechanisms which are involved in both the normal and pathological aspects of scotopic vision.

Studies on calcium-dependent macromolecular association or dissociation offer the possibility of yielding information which may be significant in interpreting the role of calcium in the changes which occur in the rod outer segment membrane following exposure to light. Another important finding by NEI scientists within the Section on Biochemistry is that calcium plays a very dramatic and central role in the excitatory process in vision. This suggests that abnormalities in calcium metabolism by ocular tissues may lead to impairment of vision. Furthermore, it may be highly significant if any pathology of vision could be understood on this basis. Also, the flourescent

probes discovered as a result of this project report the nature of the isolated visual receptor plasma membrane. This may be of use to others studying membranes, particularly those investigating the biochemistry of isolated rod outer segments. They will contribute to an understanding of the basic biochemical mechanisms which are involved in both the normal and pathological aspects of scotopic vision.

LVR investigators are studying the renewal of photoreceptor cell outer segments, a continuous process which is impaired in some pathological conditions such as progressive degeneration or developmental anomalies of the retina. The purpose of this project is the elucidation of the biochemical events involved in renewal, especially the distinction between transport of opsin to the outer segment and any further modifications of opsin necessary to produce light-sensitive disc membranes.

The indication is that opsin is transported to the rod outer segment before the vitamin A chromophore is attached to produce a light-sensitive visual pigment. The presence of pigmented epithelium does not appear to influence the rate at which the chromophore is added to newly-synthesized bovine opsin which accumulates in the outer segment.

Isolated frog retinas, on the other hand, show little accumulation of opsin and seem to add chromophore shortly after opsin is transported to the outer segment. It appears that the final steps in the outer segment renewal are regulated largely by the photoreceptors, not by the pigment epithelium. This fact has an important bearing on the identification of the cell types responsible for the defects in any of the various retinal dystrophies. Attempts will be made to demonstrate the location of rhodopsin precursors in the rod outer segments and to correlate the amount of precursor seen in frog or cow rods with specific differences in the structure of the rods.

NEI scientists have previously found that there are two types of phospholipid which are required for the structure and function of the visual pigment rhodopsin. In this project the distinct roles of these phospholipids were separately investigated.

The finding that phosphotidylethanolomine (PE) is directly involved in isomerization of all trans retinal to 11 cis retinal is probably the first instance in which a "pseudo-enzymic" function of membrane phospholipid has been demonstrated. This could provide a model reaction for phospholipid functions in other membrane systems. Another important finding of this project is that abnormal rod functions observed under certain pathological conditions, such as retinal dystrophy, may be related to degeneration of phospholipids associated with rod disc membranes. For example, phospholipid peroxidation by light has been suggested to be responsible for Turkey Blindness Syndrome, a veterinary disorder characterized by a degenerative endophthalmitis with detachment of the retina.

In the visual receptor cell, the movement of ions across its membrane and the control of this ion flow by light-released intracellular excitatory transmitter have been shown by NEI scientists to be basic in the initiation

of the light detection process of the visual system. The nature of this excitatory transmitter, how light and the visual cell control its passage across membranes, and how this transmitter in turn regulates movement of ions across the visual cell membrane are the focal points of these investigations.

The understanding of how membrane-bound proteins control the passage of materials through membranes is of foremost importance whether these materials be ions in the photoexcitatory process or ions and substrates of various sorts in the processes of development and maintenance of ocular and nervous tissue. Revelations of how visual pigments, probably the best characterized membrane protein, control movement of materials across membranes are a major contribution to biomedical research. The successful adaptation of the electron microprobe for the quantitative study of biological cells will have impact in many areas of biomedical science because it will fulfull the demand for a rapid and sensitive method for determining the ionic compositions of cells as small as one micron in diameter.

The Section on Experimental Embryology in cooperation with the Clinical Branch of NEI, the National Institute of Child Health and Human Development, and the School of Medicine at UCLA has contributed in the past year to three of the five NEI program areas: Retinal and Choroidal Diseases, Cataract, and Corneal Diseases. First, it demonstrated that the PE cells of the embryonic retina can synthesize fibrillar collagen. This gives substance to the suspicion that these cells may produce the abnormal deposits of collagen seen in such disorders as senile maculopathy and Drusen formation. Second, NEI scientists working on this project have discovered that collagen-bearing layers produced by retinal PE can induce the sclera. This focuses attention on the possible involvement of this epithelium in conditions such as blue sclerae and some colobomata.

In the past year emphasis was placed on in vitro studies extending the list of previously identified factors governing the early steps in the metaplastic regeneration of lens from the dorsal iris of newts, animals with a natural ability to regenerate a normal lens. These findings define more vigorously the in vitro conditions that optimize early steps in Wolffian lens regeneration. This project will continue to focus on the tissue interactions involved in ocular embryogenesis with emphasis on the roles played in morphogenetic foldings and induction by epithelially produced matrices.

The Section on Experimental Pathology has studied normal and pathologic eyes by light microscopy, histochemistry, transmission electron microscopy, and scanning electron microscopy. Several animal experiments are pursued for the control study of the corresponding pathologic materials.

Through the use of the electron microscope this study has revealed that microcystic dystrophy of the cornea epithelium begins with formation of an abberant basement membrane within the epithelium. The epithelial cells which are trapped beneath the abnormal basement membrane appear to undergo degenerative change and form the cyst. The epithelial layer over the basement is free from the cystic change.

It has been found that the maturation of the congenitally cataractous mouse lens cell appears to occur slower than that of the normal cell and that the earliest degenerative change, swelling of lens fibers, is found in the posterior cortical zone.

Work within this project has revealed that it is almost impossible to separate the retina from the pigment epithelium without breaking the fine microvilli of the latter cells. The attachment of the retina to the pigment epithelium appears to be firmer than generally thought. This information is important for understanding the pathophysiology of retinal detachment.

Detailed study of pathologic materials is one of the most basic and important tasks in biomedical research. This laboratory is one of a few which are capable of pursuing this type of research on pathologic eye materials.

Also within the Section, retinas of normal rhesus monkeys have been photocoagulated by a ruby laser following the technique identical to that of the clinical application. The animals were sacrificed at several time intervals and the retinas studied histologically, electron microscopically, and by trypsin digestion technique for retinal blood vessels.

Although necrotic changes in the photoreceptor cells and the pigment epithelium in each burn lesion are extensive, the retinal tissue appears to tolerate the treatment rather well. Each lesion is sharply circumscribed and the repair process seems to take place within the damaged area. The structure of the retinal tissue between the burns is not disturbed at all. No appreciable swelling or cell infiltration has been seen in this normal area. This treatment appears to remove a great number of photoreceptor cells from the retina. The simplification of the tissue may be the reason for the clinically beneficial effect of this treatment. Small numbers of surviving retinal cells seem to be sufficient to maintain the normal functions of the retina. The findings of the present study favorably support the use of photocoagulation therapy. The multiple laser burn appears to be safe to the retinal tissue.

Among several important contributions in the recent retinal studies, demonstrations of the morphologic changes of the outer segment membranes by light and of the renewal mechanism of the photoreceptor cells appear to be most significant. Retinas of the rhesus monkeys were exposed to continuous flashes of light (ten per second) by an electronic strobe light installed in the lamp house of an ophthalmoscope. The animals were divided into two groups. One group was exposed for one hour and the other for three daily 30-minute exposures. Animals were examined by electron microscope at various time intervals after the exposure.

All exposed retinas began to show pathologic changes in the outer segments starting on the second day. Two days after the one hour exposure the plasma membrane of the outer segment was fragmented and vesiculated and the stack of the disc membranes became irregular. After the three 30-minute exposures the outer segments formed knots a few microns away from the ciliary

junction. The outer segments closest to the inner segment, which are believed to be newly formed portions, were found to be larger than the distal halves. This suggests that mild repeated stimulation resulted in hypertrophy of the outer segments.

These changes have been found to stay in the retina for a long period of time. Irregular arrangement of the outer segments was found one year after the exposure. Also, a small number of photoreceptor cells in the exposed area began to degenerate in the later period.

It is common to find pathologic changes which are identical to those of the present experiment in the outer segments of "normal" human retinas, particularly at the macular zone. These findings indicate that the human retina may accumulate photic changes with time and that along with certain other factors, photic damage may induce macular degeneration.

The mechanism and site of aqueous formation remain major questions in eye physiology and are important to understanding the pathogenesis. The function of each layer of the ciliary epithelium, which has not been clearly shown, is to be demonstrated by another LVR project using rhesus monkeys. Fine structure of the ciliary epithelium has been studied after alteration of the intraocular pressure in various conditions and durations. The most extensively performed experiment during the past year has been the perfusion of the internal carotid artery with hypertonic solution. The accumulating information from this study is significantly approaching a newer understanding of the function of the ciliary epithelium. The future course of the project will attempt to pinpoint the function of the non-pigmented epithelial cell.

Drugs which destroy cell microtubules reversibly are among those which are used commonly in cancer chemotherapy. It is essential for us to understand the precise functions of microtubules in ocular cells if we are to determine accurately the dosage levels of anti-cancer drugs which are safe for the maintenance of normal vision. Microtubules are conspicuous components of developing lens cells, inner segments, filament regions of photoreceptor cells, and nerve axons. It is conceivable that drug overdose could lead to cataract formation if it destroys the microtubules in an elongating lens cell during a critical period. Likewise, vision may be impaired by disruption of microtubules in photoreceptors and axons. This study should help determine if any of these ocular cells, which depend on microtubules and microfilaments for their normal function, may be sensitive to chemotherapy and other environmental or hereditary insults.

The Section on Experimental Pathology studied the ultrastructure and function of the pigment cells of the eye, the purpose of which has been to investigate and define more precisely the intimate physical and chemical interrelationships that exist between the pigmented cells and the visual cells of the eye. LVR scientists have utilized an hereditary pathological condition as an experimental tool to investigate how the membrane discs of the rod outer segments are digested by the pigment epithelium. Analyses of normal and mutant cells have been carried out by light microscopy and modern techniques of high resolution electron microscopy as well as cytochemistry at

both levels.

Cytochemistry at the electron microscope level has enabled the investigators to localize within the pigment epithelial cells and choroid cells the enzymes that are involved (acid phosphatoses and catalases). Differences in the packaging of these enzymes by normal and mutant pigments epithelial cells permit a greater definition of the steps involved in the formation of crysosomes and melanosomes. NEI scientists have shown that there is more relation between these processes than previously known. Such studies on pigmented cells of the eye contribute directly to our understanding and managing of many retinal and choroidal diseases.

Studies on the physiology of the primate visual system were conducted within the Section on Neurophysiology during FY 1974. Experiments were completed on the analysis of graded, visually evoked extracellular and intraocular response from the foveal region of the striate cortex of anesthetized, paralyzed rhesus monkeys. The findings show that the earliest electrical responses detectable in the foveal striate cortex, following light stimulation, is a graded extracellular potential which is positive at the cortical surface and negative in the gray matter and has a peak latency of about 60 msec. The response is similar at both on-and-off-phases of a light stimulus. There are indications that all three cone mechanisms participate in this response. Each cone mechanism contributes a similar potential to the response but antagonisms between cone mechanisms is apparent. The proportion in which a cone mechanism contributes to the response varies from one area to another. This implies topographical differences in the representation of cone mechanisms in the striate cortex.

Such studies of retinal function at the cellular level should prove valuable for understanding vision and the pathophysiology of retinal diseases.

At least three independent information-processing systems have been distinguished in the primary visual cortex of the rhesus monkey. The majority of color sensitivity cells respond without regard to stimulus shape or direction of movement. Cells in a second group respond only to very slowly moving, precisely oriented light bars without regard to color or direction. Cells in a third group respond preferentially to stimulus movements in one direction, without regard to color or line orientation. Most cells in this area of the visual cortex (area 17) are thus specialized for the detection of a single stimulus feature at the expense of other features.

The color cells tend to be located in two distinct regions (layers 3B and 4B) near the termination sites of lateral geniculate axons. Directional cells are usually found in layer 4A, which contains axon terminals from adjacent cortical regions. Orientation-specific cells tend to occur in the upper and lower most layers (2, 3A, 5, and 6).

It is essential that scientists understand the normal mechanisms of information-processing in the visual cortex before they attempt to define the nature of the visual defect in such conditions as congenital cataract, strabismus, astigmatism, some types of color deficiency, the aphasias, and

disorders of reading (for example dyslexia) in children.

In cooperation with the University of Vienna in Austria, the Section on Biochemistry of LVR, and the Laboratory of Biochemical Genetics at the National Heart and Lung Institute, scientists from the Section on Neurophysiology have devised a preparation of the cat retina which has allowed them to make intracellular recordings from most of the neuronal types therein and to stain the neurons with procion yellow dye. This marks the first time that such techniques have been successfully applied to any mammalian retina. The responses of "A" and "B" type horizontal cells, horizontal cell axon terminals, both rod and cone bipolar cells, two distinct types of amacrine cells, and several classes of ganglion cells have been identified.

Horizontal cells have been shown to have unusual properties which may prove to be broadly significant to our understanding of the central nervous system. One such astonishing finding was that the axon terminal of the "B" type horizontal cell has responses which are unrelated to those found in its cell body. Whereas only 40% of the amplitude of the cell body response is generated by rods, 80% of the amplitude of the axon terminal response is generated by rods. Furthermore, the rod signal of the axon terminal has been shown to be over one log unit more sensitive than that of the cell body. Thus the "B" type cell body and its axon terminal system appear to be functionally independent units. Other neuronal types are currently under intensive study and it seems possible that an exhaustive description of neuronal properties in the cat retinal may emerge in the next few years.

LABORATORY OF VISION RESEARCH
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[illegible]

REPORT TO THE [illegible]

[illegible]

[illegible] was enlarged to a wide variety of [illegible] to improve [illegible] diagnosis, determination of the extent of disease, [illegible] of factors related to risk and to active investigation of alternative treatments. These involved a combination of direct research activities -- the staff and assistance in consultation to others in the field of human research. In addition, efforts were directed toward the education of research workers in clinical investigation to participate in the [illegible] and methodologic methods. Although the present staff is too small to make satisfactory progress with all of the projects offered, plotting or beginning [illegible] educational activities are still incomplete. I have one of the highest priorities [illegible] improvement in the quality of clinical eye research in the future [illegible] will depend in large part on the success of this [illegible] educational effort.

The [illegible], in collaboration with the Division of Health Examination Statistics, National Center for Health Statistics, continues to analyze data on eye diseases from the National Health and Nutrition Survey. This analysis will make it possible to determine the prevalence of visual disorders in a random sample of Americans and to study possible associations of eye problems with nutritional deficits and different diseases.

[illegible] tests to [illegible] areas of the continental United States between the ages of [illegible] and [illegible] were the full examination which [illegible] from [illegible] procedures which were used [illegible] for the clinics. The eligible [illegible] of those to whom the examination was offered is [illegible] percent. Clinic examiners were [illegible] of house staff and research fellows from various academic institutions across the [illegible] and research facilities.

This is the first attempt to determine the prevalence of visual disorders in the American population based on examination sufficient to meet criteria. It will provide a measure of the status of ocular health here and directions for future areas of continued research.

The Office of Biometry and Epidemiology has also continued its coordination of the Framingham Eye Study in cooperation with the Epidemiological Research Section of the National Heart and Lung Institute, the Department of Preventive Medicine and Epidemiology of Boston University School of Medicine, and the Department of Preventive Medicine, Harvard University School of Medicine.

The purpose of the investigation is to identify [illegible] among those who participated in the Framingham heart study [illegible] of the present time here one or more of the four most common causes of [illegible] in [illegible] people

cataract, senile macular degeneration, glaucoma, and diabetic retinopathy. In addition to determining the prevalence of these diseases, the Office of Biometry and Epidemiology is attempting to relate eye measurements to present disease status in an effort to identify risk factors. As a guide to prevention of these eye diseases, it would be most helpful to identify risk factors associated with them.

An ocular examination similar to that of Framingham, with replications by an NEI ophthalmologist in Framingham, is being carried out under contract with Boston University in the vicinity of the original Framingham Heart Study cohort to identify the natural history of these diseases. Additional information will be obtained from medical data accumulated over the previous twenty years on members of this group in the National Heart and Lung Institute.

The NEI provides statistical consultation for the Cooperative Diabetic Retinopathy Study which is being conducted in seven cities from sixteen medical centers. The study is a randomized control trial to determine whether photocoagulation can delay the onset or lessen the severity in proliferative diabetic retinopathy. NEI's statistical consultation is in matters of organization, design, conduct, data collection, and data analysis. The objectives are to assure adequate control of the trial, to develop methods of patient recruitment, to develop research procedures to minimize or eliminate sources of bias and to quantify any residual bias, to assure uniformity of terminology, definitions, and standardization of methodology, to assess reproducibility of vision examination, to monitor adherence to protocol and completeness of patient studies and follow-up, and to advise on data editing, monitoring, and analysis.

Through the end of June [illegible] patients of the recruitment target of 1,600 had entered the study. Critical to the success of the study, in addition to the adequate number of patients with diabetic disease, are adherence to protocol and prevention of dropouts - those who fail to return for periodic examinations or, since only one eye is randomly selected for treatment, those who receive treatment at the onset. Even patients of the study will be closely monitored.

An NEI staff member has compiled a registry of over 700 pairs of monozygotic (MZ) and dizygotic (DZ) twins for the purpose of longitudinal investigations on the heritability of ocular characteristics, case-control studies, and studies of the early natural history of chronic disorders. Comparison of agreement among pairs of twins with respect to ocular characteristics is valuable as an indication of the relative role of heredity and environment in the expression of these characteristics. This registry serves as a resource to identify appropriate populations for such studies as well as for investigations of therapeutic effectiveness.

NEI is also conducting a three-year study of a population of 55 pairs of young monozygotic twins who are myopic (near-sighted). The co-twin receives standard spectacle correction at the outset. The other is managed using specially prescribed bifocal spectacles and topical short-acting cycloplegic eye drops instilled upon retiring at night. The essential advantages in working with MZ twins in this investigation lies in the immediate match on

genetic constitution for the treated twin and his co-twin control. This study will provide a careful appraisal of the effectiveness of a clinically acceptable method of controlling accomodation.

Other OBE studies relating to twins include: a thorough description of biases and other methodologic problems which might adversely influence the accuracy and validity of twin heritability studies, an attempt to assess the role of genetic factors in determining normal levels of intraocular pressure and in determining the size of the physiologic cup of the optic nerve head as measured by a horizontal cup/disc ratio, and to assess the role of genetic factors in determining the intraocular pressure response caused by topical application of corticosteriod eye drops.

The Association of University Professors of Ophthalmology (AUPO) Workshop on Clinical Trials was conducted by OBE to familiarize clinical investigators with methods of good clinical trials. A panel discussion and six presentations: ethics, control group and randomization, objective measures and double-masking, reproducibility of measurements, writing a protocol, and practical applications were held at the AUPO meeting in November, 1973. The presentation and discussions were tape recorded and submitted to the authors for editing. All materials have been edited, and the manuscript is being submitted to the American Journal of Ophthalmology for publication.

In addition to these activities, OBE prepared a booklet containing information supplied by sixteen states which made up the Model Reporting Area for Blindness Statistics (MRA). Over a period of eight years each state voluntarily maintained a registry of its blind. In the booklet OBE classified persons added to each state's blind registry according to their age, color, sex, visual acuity, age when blinded, causes of blindness, and other factors. Although the data is uniform from state to state and has been very useful to NEI, there are no immediate plans to continue the MRA since little additional knowledge will be gained from its continuence. Efforts are under way, however, to make use of MRA data for designing studies directed toward better understanding those factors which are associated with the major causes of blindness in the United States.

OFFICE OF BIOMETRY & EPIDEMIOLOGY
PUBLICATIONS

Aiello, L.M., Berrocal, J., Davis, M.D., Ederer, F., Goldberg, M.F., Harris, J.D., Klimt, D.R., Knatterud, G.L., Margherio, R.R., McLean, E.N., McMeel, J.W., Myers, F.L., Norton, E.W.D., Patz, A., Prout, T., Riekhof, F.T., Straatsma, B.R., Tasman, W., vanHeuven, W.A.J., Watzke, R.C.: Diabetic Retinopathy Study. (Letter to the Editor) Am. J. Ophthalmol. 76: 403-405, 1973.

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ANNUAL REPORT
OFFICE OF SCIENTIFIC REPORTS AND PROGRAM PLANNING COORDINATION
July 1, 1973 - June 30, 1974

The NEI Office of Information was redesignated as the Office of Scientific Reports and Program Planning Coordination during the year, reflecting both the reorganization of public affairs activities within HEW and the Institute's own decision to centralize program planning activities within the Office of the Director.

PUBLIC AFFAIRS CUTS AND REORGANIZATION

On July 19, HEW Secretary Weinberger issued a memorandum calling for the reduction in the amount of "self-serving, promotionally oriented material in Government." Each agency was allowed to present its case on which of its information activities could be considered "public affairs" (defined by HEW to include such public relations functions as publicity, press relations, films, exhibits, and other agency-initiated promotional projects) and which were not. The Eye Institute supported NIH's argument, which HEW eventually accepted, that its information program is largely concerned with answering public inquiries, scientific and technical reports, and consumer health education. Recognizing this, the Eye Institute, as well as other Institutes at NIH, were asked to identify staff members whose functions were associated with public affairs activities. One public affairs staff member from this Office was identified who, according to HEW guidelines, was transferred to another high-priority area (Extramural) within the Institute. The remaining staff were identified by the Institute as having non-public affairs information responsibilities, a classification which was accepted by NIH and the Department.

The above reclassification and transfer resulted in a centralization of all Institute/Division public affairs activities in the Office of the Director, NIH. Because public affairs was never a major NEI activity, the information activities of the Office have continued generally as before.

A second part of the public affairs reorganization was the reduction in the number of HEW publications. As a result of the Departmental request, NEI identified three of its twelve publications to be eliminated, but retained temporary authority to publish its experimental newsletter, 20/20.

Aside from consuming a considerable amount of staff time in responding to numerable memoranda from NIH and HEW, the impact of the public affairs reorganization on the National Eye Institute has been minimal: no high priority publications were eliminated, and we have been allowed to continue our information activities as in the past with a few minor exceptions.

PUBLIC INFORMATION

Publications

Partly as a result of uncertainty concerning the fate of publications during the public affairs reorganization, no new fact sheets or health education booklets on eye disorders were published during the year. An HEW-initiated project to produce a booklet on eye care (as reported in last year's Annual Report) was temporarily shelved due to uncertainties within the Office of Consumer Affairs, HEW, over the future of its consumer publications series of which the booklet was to be part. An attempt will be made during the coming year to publish the completed manuscript for this booklet as an NEI publication.

In cooperation with NEI Extramural and Collaborative Programs, two new folders on extramural support programs (Special Visual Sciences Research Award Program and Specialized Clinical Research Center Grants) were prepared. Two issues of 20/20 were mailed to the vision research community. Whether or not the Institute is permitted to continue this publication depends on the result of a readership survey which will have to be undertaken in the next issue prior to obtaining formal OMB approval.

The following number of NEI publications were distributed during the year:

Cataract (booklet and fact sheet)	3,926	Retinal Detachment	2,881
Diabetic Retinopathy	3,126	Refractive Errors	2,835
Retinitis Pigmentosa	2,841	Glaucoma	3,301
Macular Degeneration	2,849	Corneal Disease	2,673
Statistics on Blindness in the Model Reporting Area, 1969-1970			367
Corneal Disease Task Force Reprint			21
U. S. News and World Report Interview with Dr. Kupfer			200
Blindness and Services to the Blind in the United States (OSTI Report)			267
Security is an Eye Patch			48,120

Requests for the latter publication, supplies of which were inherited from the former PHS Neurological and Sensory Diseases Control Program, were stimulated by an announcement of its availability mailed to the nation's ophthalmologists by the American Association of Ophthalmology. Over 450 requests from practicing ophthalmologists for multiple copies were received, resulting in the near depletion of supplies of this very popular booklet. Over the past three years, the Institute has distributed over 240,000 copies of Security is an Eye Patch.

Public Inquiries

Approximately 800 written inquiries received by the Office required an individually written response, whereas the number of telephone inquiries

increased by approximately 33 percent: over 2,400 telephone calls were handled during the year. The majority of inquiries concerned cataract, both research and treatment. In particular, there was great public interest in phacoemulsification and the role of nutrition in cataractogenesis and prevention. Other areas of interest concerned laser treatment of glaucoma and diabetic retinopathy and the possibility of individuals coming to the National Eye Institute for treatment. Replies to approximately 160 letters from the public expressing concern with the Institute's support of diabetes-related research were prepared.

The Office responded to 35 controlled, written Congressional inquiries, and 96 telephone calls from Congressional offices.

Press Relations

Five press releases were prepared (new members of the National Advisory Eye Council, a warning of the possible damage to the eye when observing the Comet Kohoutek's approach to the sun, announcements of the appointments of Dr. Nusser and Mr. McManus, and Dr. Kinoshita's receipt of the ARVO Proctor Medal.) Eight stories were prepared for the NIH News and Features service, mailed to science writers in the professional and general press. Ten stories were prepared for the NIH Record. Announcements were mailed to the vision research journals concerning new NEI grants and awards, the availability to investigators of breeding pairs of rats with inherited retinal degenerations (produced under an NEI contract), and other items of immediate interest to the vision research community.

The Office assisted press representatives from the Associated Press, U. S. News and World Report, Readers Digest, the Blue Sheet, Woman's Day, Medical World News, National Enquirer, U. S. Medicine, and Medical Tribune.

Miscellaneous

In cooperation with the Office of Biometry and Epidemiology, the Office helped coordinate arrangements for presentation of a workshop on clinical trials, in conjunction with the winter meeting of Association of University Professors of Ophthalmology. The Office also coordinated arrangements with the Laboratory of Vision Research and Clinical Branch for a tour of the Institute by AUPO members.

A public relations proposal concerning the Framingham Eye Study was prepared. Its primary objective is to help enhance patient recruitment efforts for the study and to provide means for informing the professional and lay publics of the importance of this investigation. Thus far, a radio spot announcement was prepared and distributed in the Framingham and Boston areas, encouraging those who had participated in the Framingham Heart Study to take part in the Eye Study as well. Letters encouraging participation in the study have also been drafted and will be mailed to prospective participants. Finally, a supplement to the NIH science writers service, News and Features, was being prepared for distribution to the press and to members of the Study. This activity will be pursued further in FY 1975.

Four Search for Health columns were prepared for the NIH Office of Information concerning terminology relating to the eye, eye diseases, eye disease diagnosis, and methods of treatment which were mailed to weekly newspapers across the United States.

Arrangements were made in cooperation with the NIH Office of Information for Dr. Kupfer's appearance on a Tampa, Florida, television talk show in conjunction with the Spring ARVO meeting in Sarosota. The Office coordinated arrangements for interviews with Dr. Kupfer by the Readers Digest, U. S. News and World Report, U. S. Medicine, and the American Optometric Association News.

The Annual Save Your Vision Week Presidential Proclamation was prepared. NEI's contributions to the NIH Almanac and NIH Annual Report were prepared. The Office coordinated Institute submissions to the NIH Scientific Directory and Bibliography as well as this Annual Report.

Assistance was provided to the Director in the preparation of presentations before the Association of University Professors of Ophthalmology and the Association for Research in Vision and Ophthalmology.

PROGRAM PLANNING COORDINATION

Following recommendations of the NEI management conference held last September, the then Office of Information was designated as the coordinating point within the Institute for program planning and development activities. The Information Officer, Julian Morris, was designated as the Planning Coordinator. Although the Information Office had been actively engaged in planning activities, this designation reflected the Institute's desire to formalize its planning activities and provide better organization and followup.

The Office has thus had major responsibility for preparation of the NEI Forward (Long Range) Plan as well as special planning documents required by NIH and HEW. It has also: worked with the Executive Officer and Budget Officer in the drafting of narrative materials related to Appropriations Hearings, developed materials for various presentations to NIH staff regarding program plans, in cooperation with other segments of the Institute documented specific needs for additional funds and positions, coordinated arrangements for the Cataract Workshop, and assisted in the arrangements for the National Advisory Eye Council Program Planning Committee's review of the Retinal and Choroidal Diseases, Cataract, and Corneal Disease programs.

For the coming fiscal year, the Office has major responsibility for coordinating the Committee's review of the Glaucoma and Sensory Motor Disorders program and in following through on the Committee's activities to the drafting and publication of its final report.

Clinical Branch

Ballintine, Elmer J., M.D.
Ocular Hypertension Study
Aqueous Humor Formation in Monkeys

Bergsma, Donald R., M.D.
Studies of Choroidal-Retinal Degenerative Diseases
Studies of Ophthalmic Familial and Genetic Diseases

Charles, Steve, M.D.
Development of Improved Instrumentation for Vitreous Surgery

Eichenbaum, Daniel M., M.D.
Combined Clinical and Experimental Animal Study of the Pathogenesis of Abnormal Proliferations in the Vitreous Cavity

Foon, Kenneth, M.D.
Inheritance of Susceptibility to Lymphocyte Transformation Inhibition

Frank, Robert N., M.D.
Argon Laser Photocoagulation of Retinal and Choroidal Diseases
Biochemistry of Vertebrate Retinal Receptor Outer Segments

Gaasterland, Douglas E., M.D.
Study of the Use of Radioiodinated (I-125) Chloroquine Analog for the Differential Diagnosis and Detection of Intraocular Melanoma
Experimental Glaucoma in the Rhesus Monkey

Gunkel, Ralph D., O.D.
Design and Construction of Ophthalmic Instruments; Research in Methods of Evaluating Visual Processes

Kolb, Helga, Ph.D.
Anatomy and Pathology of the Mammalian Retina

Kupfer, Carl, M.D.
Studies of Parameters of Intraocular Pressure

Macri, Frank J., Ph.D.
Study on the Pharmacodynamics of Various Agents Affecting the Intraocular Pressure

Clinical Branch (cont.)

Ross, Karyn
Ciliary Body Blood Flow and Aqueous Humor Formation in the Rhesus Monkey

Sullivan, William R., M.D.
Comparative Treatment of Bullous Keratopathy with the Bausch and Lomb "Soflens" and the American Optical "Bandage" Soft Contact Lenses
Studies of the Effect of Histocompatibility (HL-A) Testing and Corneal Transplantation
Treatment of Keratoconjunctivitis Sicca with N-acetyl-l-cysteine

Laboratory of Vision Research

Section on Biochemistry

Kinoshita, Jin H., Ph.D.
Chemistry and Metabolism of the Lens
Cataracts

Chader, Gerald J., Ph.D.
Biochemical Development and Function of Retina and Pigmented Epithelium
Cyclic Nucleotides and Vision

Helmsen, Ralph J., Ph.D.
Induction of Buphthalmos in Chicks by Feeding a High Level of Glycine
Chemistry of the Cornea
Mechanism of Herpes Simplex Virus Infection of Corneal Cells

Hess, Helen H., M.D.
Biochemical Composition of Photoreceptor, Neuronal and Glial Cells of Normal and Pathological Retina and Brain

Lewis, Marc S., Ph.D.
Chemistry of Rhodopsin
Physical Chemistry of Model Gel Systems

O'Brien, Paul, J., Ph.D.
Synthesis of Sugar-Containing Polymers in Retina
Protein Synthesis in the Retina

Shichi, Hitoshi, Ph.D.
Biochemistry of Visual Pigments

Laboratory of Vision Research (cont.)

Section on Experimental Embryology

Coulombre, A.J., Ph.D.
Ocular Morphogenesis

Section on Experimental Pathology

Kuwabara, Toichiro, M.D.
Anatomic and Pathologic Studies of Ocular Tissue
Effect of Laser on the Retina
Light Effect on the Retina

Okisaka, Shigekuni, M.D.
Effect of Intraocular Pressure on the Ciliary Epithelium

Robison, W. Gerald, Jr., Ph.D.
The Functions of Cell Microtubules and Microfilaments in Ocular Tissues
Ultrastructure and Function of the Pigment Cells of the Eye

Section on Neurophysiology

Gouras, Peter, M.D.
Physiology of the Primate Visual System

Dow, Bruce M., M.D.
Information Processing in the Visual Cortex of the Rhesus Monkey

Nelson, Ralph, Ph.D.
Electrophysiological Studies of Mammalian Retina

Office of Biometry and Epidemiology

Office of the Chief

Kahn, Harold A.
The Model Reporting Area for Blindness Statistics
National Health and Nutrition Survey
Framingham Eye Study
Comparison of Localized Treatments for Bilateral Disease

Ganley, James P., M.D., Dr.P.H.
Systemic and Ocular Onchocerciasis
Lymphocyte Transformation Response in Presumed Ocular Histoplasmosis

Office of Biometry and Epidemiology (cont.)

Section on Clinical Trials and Natural History Studies

Ederer, Fred
- Statistical Consultation, Collaborative Diabetic Retinopathy Study
- Assessment of Evidence on the Value of Photocoagulation in Treating Diabetic Retinopathy
- ACPO Workshop on Clinical Trials
- Patient Bias, Investigator Bias, and the Double-Masked Procedure
- Confidence Limits on the Ratio of Two Poisson Variables

Section on Mathematical Statistics and Computer Applications

Milton, Roy C., Ph.D.
- Statistical Summary of Dark Adaptation and Retinal Function Clinical Data

Remler, James P., M.D., Dr.P.H.
- Accuracy and Repeatability of Reading Fundus Photographs

Miller, Rita
- Prevalence, Incidence and Economic Cost of Eye Disease in the U.S.

Kahn, Harold A.
- Bayesian Statistical Theory and Methods: A Critical Study

Section on Ophthalmic Field and Developmental Research

Schwartz, J. Theodore, M.D.
- Twin Register for Eye Examinations (TREE)
- Effect of Treatment on the Progression of Myopia
- Methodology of Twin Heritability Studies
- The Influence of Methodologic Differences on Measurements of Cup/Disc Ratio
- Frequency Distribution of Horizontal Cup/Disc Ratio and Relationship Between Cup Size and Other Clinical Variables
- Association Between the Ocular Hypertensive Response to Topical Dexamethasone and Other Clinical and Laboratory Measurements
- Twin Study on the Inheritance of Normal Levels of Intraocular Pressure
- Twin Heritability Study of Horizontal Cup/Disc Ratio in Normal Eyes

Office of Biometry and Epidemiology (cont.)

Section on Ophthalmic Field and Developmental Research (cont.)

Reuling, Frank E., M.D.
Heritability of the Effect of Corticosteroids on Intraocular Pressure