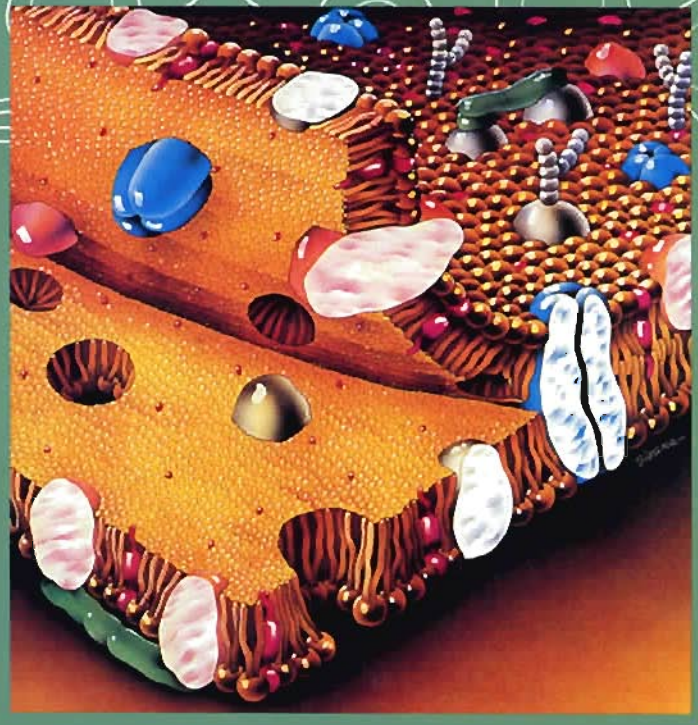
Ernest C. and Yvette C. Villere Chair For the Study of Retinal Degeneration

January 1992

Louisiana State University School of Medicine and the LSU Eye Center
New Orleans



Allen A. Copping, D.D.S.
President of the Louisiana State University System

Perry G. Rigby, M.D.
Chancellor of the Louisiana State University Medical Center

Robert S. Daniels, M.D.
Dean of the School of Medicine in New Orleans

Herbert E. Kaufman, M.D.
Boyd Professor and Head of Ophthalmology
Professor of Pharmacology and Experimental Therapeutics

Nicolas G. Bazan, M.D., Ph.D.
Ernest C. and Yvette C. Villere
Professor of Ophthalmology,
Biochemistry and Molecular Biology,
and Neurology
Director
Neuroscience Center of Excellence

Dedication

Mr. Ernest C. Villere's dedication and untiring efforts toward the establishment and advancement of retinal research led to the endowment of the Ernest C. and Yvette C. Villere Program on Retinal Degenerations at the Eye, Ear, Nose and Throat Hospital, with the support of the EENT Foundation. A decisive force for the establishment of this Chair was the influence and inspiration provided by Professor Herbert E. Kaufman. Since 1981, I have carried research supported by this program. It is both an honor and a privilege for me to accept today the Ernest C. and Yvette C. Villere Professorship of Ophthalmology, and I am grateful that I can use it for the betterment of humankind.

Mr. Ernest Villere's keen insight and sensitivity allowed him to recognize the fact that retinal degenerations are a leading cause of blindness, and that the only way to prevent and treat these blinding diseases is through research. For it is only through studies such as those funded by the Chair that discoveries about the ultimate mechanisms of blinding disease are made. The findings from this research may eventually lead to the development of effective treatments, and perhaps even preventive regimens and cures, for these devastating diseases.

I would like to express my deep gratitude to the family of Mr. and Mrs. Villere for all that they have done over the past years to establish the retinal degeneration research program. Through their enthusiastic pursuit of funding for this program, as well as through the family's own generous donations, a significant amount of progress in this field has been accomplished. Mr. Villere had an uncanny understanding of the myriad details involved in launching a highly specialized research program that is rarely seen in people who are not scientists. The human greatness that he personified has inspired our research team to work even harder to achieve the goals that were so important to him. Our commitment has been strengthened, and we aspire to return as much knowledge to humanity as we can through our research programs.

The friendliness, sensitivity, and creativity of Mr. Villere have been admired by all those whose lives he has touched. Because of the personal quality of foresight, he was a true visionary. The result of his vision is our research laboratory, a laboratory where great strides have been made to alleviate some of humankind's most tragic diseases. Although the world has lost a great benefactor and humanitarian, the death of Mr. Villere does not stop us all from benefiting from the fruits of his zealous campaign against blinding diseases. Mr. Villere served humankind well through his generosity and altruism; he continues to do so through the research performed under the auspices of the Villere Chair.

It is to Ernest C. and Yvette C. Villere that this book is dedicated.

Nicolas G. Bazan, M.D., Ph.D.
Ernest C. and Yvette C. Villere Professor of Ophthalmology
Professor of Neurology and
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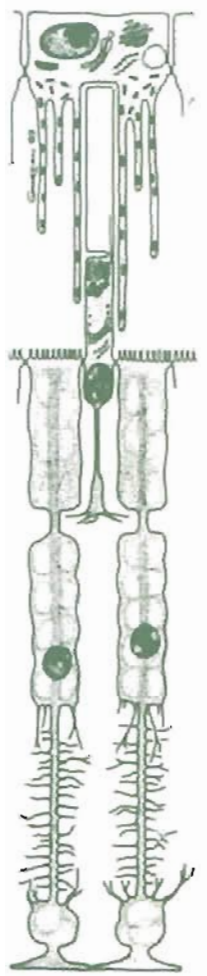
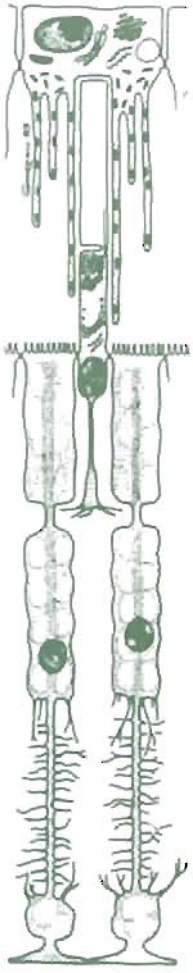


Ernest Caliste Villere

Ernest Caliste Villere was born in New Orleans in 1904. After attending Tulane University, he went to work for Burroughs Adding Machine Company as a salesman. In 1927, he joined St. Denis J. Villere and Company, an investment counseling firm founded by his father in 1911. He became a partner a year later and remained there until his death at age 82 in 1986. Mr. Villere married Yvette Chequelin, and they raised two sons and a daughter, St. Denis, George, and Mathilde, who gave them thirteen grandchildren and four great-grandchildren.

Mr. Villere, who was Vice-President and served on the Board of Directors of the Historic New Orleans Collection, was an avid New Orleans historian. This is partly due to the fact that the Villere family played a major role in the establishment and growth of New Orleans. For example, his great-great-great-grandfather, Etienne Roy de Villere, accompanied Pierre Le Moyne, Sieur d'Iberville, on his first voyage to the Mississippi River in 1699, and his great-great-grandfather, Jacques Philippe Villere, was Louisiana's first native Governor. The Governor's son was the one who, after seeing troops approaching from the family plantation in Chalmette, warned General Andrew Jackson in New Orleans that the British were approaching the City.



Mr. Ernest Villere was instrumental in obtaining for the Historic New Orleans Collection the papers of Pierre Clement de Laussat, the French administrator who helped transfer the Louisiana Territory from France to the United States in 1803. Mr. Villere was also a member of the Society of the Founders of New Orleans, the Society of the War of 1812, and the Society of the Sons of the American Revolution.

Throughout his lifetime, Mr. Villere served on numerous educational and governmental boards and committees, and was very active in the Roman Catholic Church. He was the founder and first president of the Financial Analysts of New Orleans, a member of the New York Society of Financial Analysts, a founder and treasurer of Valencia, Inc., a social club for teenagers, a treasurer of the Sierra Club, a founder and director of the Public Affairs Research Council and the Bureau of Governmental Research, a director of the Metropolitan Area Committee, the Information Council of America, and St. Mary's Dominican College, and a trustee of the Holy Name of Jesus Parish. His philanthropic activities were acknowledged repeatedly, and he received many commendations and awards for service rendered to these various groups, including the *Pro Ecclesia et Pontifice* medal, an award for service to the Church and the Papacy, and the Order of St. Louis IX, King of France, for his work in the Archdiocese. He was the vice-chairman of the fund-raising drive for Hôtel Dieu Hospital, a trustee of the Alton Ochsner Medical Foundation and the Libby-Dufour Foundation, and a board member and secretary of the Eye, Ear, Nose and Throat Hospital. He reigned as Rex, King of Carnival, in 1968.

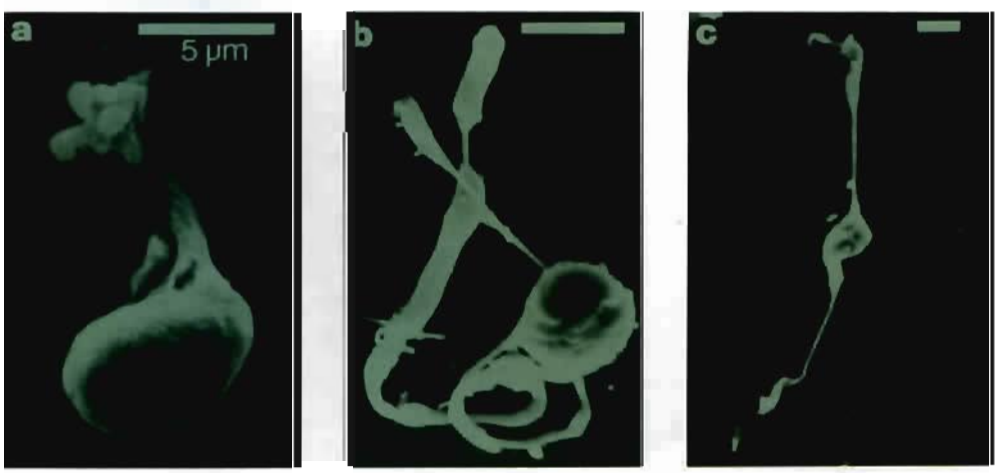
Mr. Villere died November 1, 1986 at the age of 82.

Yvette Chequelin Villere

Yvette Chequelin Villere, a volunteer for numerous charitable organizations, was a lifelong resident of New Orleans. She attended the University of Wisconsin and graduated from Newcomb College in 1928. She studied social work at Tulane University in 1929 and participated in a summer program at the University of Sorbonne in Paris in 1931. She taught French at the Newcomb Nursery School and the Metairie Park Country Day School from 1930-35. She was a medical volunteer at Touro Infirmary Clinic, a volunteer social worker for the Bureau of Transients and Homeless, a board member of the Travelers' Aid Society, a board member of Le Petit Salon, a board member and founding member of Valencia, chairwoman of the Women's Division Community Chest in 1942 and a volunteer chairwoman for the Tulane and Newcomb Foreign Students Hospitality organization. She headed the Junior League Thrift Shop in 1934, headed the summer play session for the Junior League Community Center, headed the Junior Series for the Junior League, started a Cub Scouts organization at Holy Name School, started a Junior Girl Scouts (Brownie) organization at Sacred Heart Academy, headed the Mercy Hospital fund drive, and started the Friday night square dances at Holy Name School.

Mrs. Villere died April 23, 1991 at the age of 83.

Mr. and Mrs. Villere established the Ernest C. and Yvette C. Villere Chair for the Study of Retinal Degeneration to study retinitis pigmentosa, a degenerative disease of the retina that leads to blindness. Their son George has suffered from this disease.



Photoreceptor cells seen by the scanning electron microscope. In c an abnormal cell affected by retinal degeneration. Compare with the normal cell in b.

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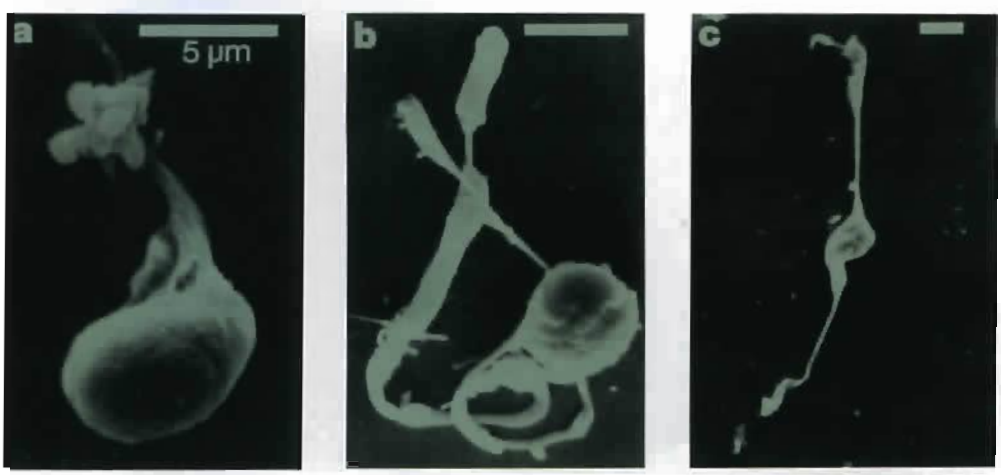

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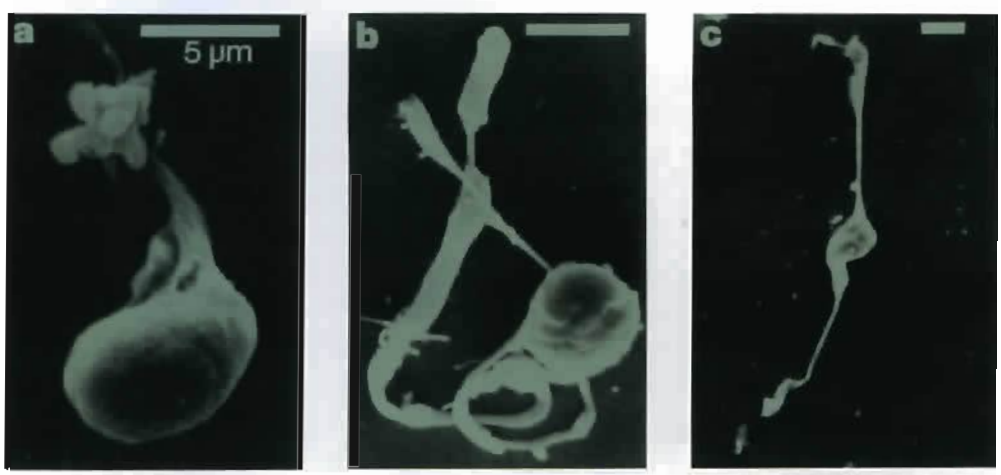

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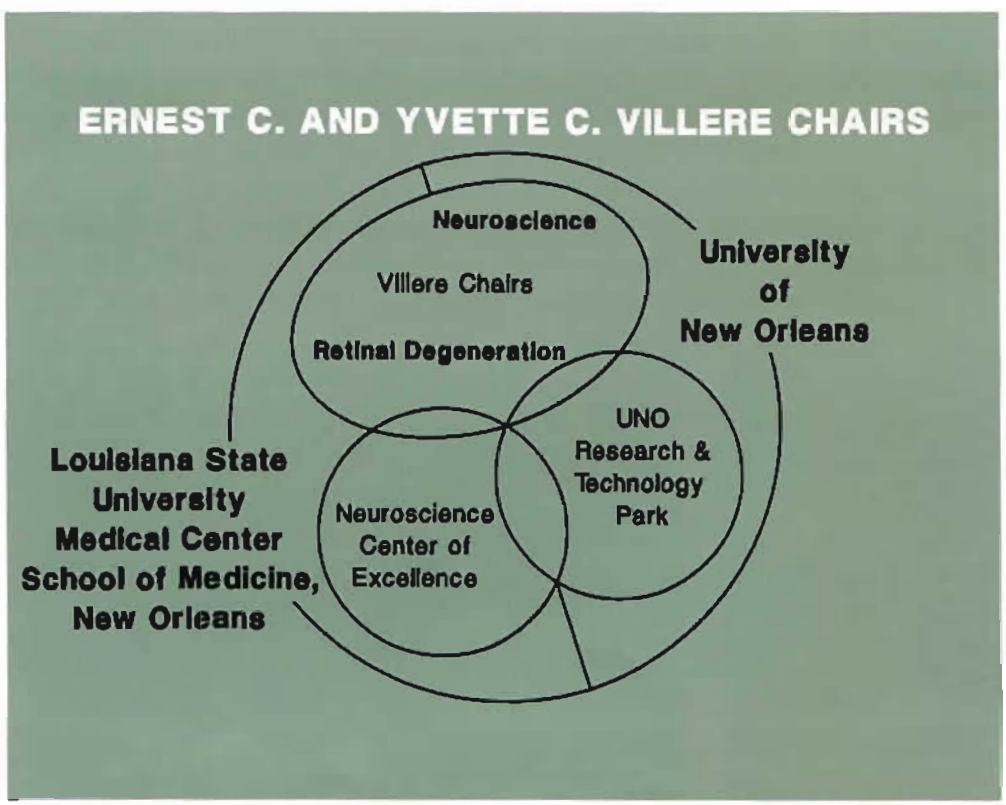
OVERVIEW

Introduction

The Ernest C. and Yvette C. Villere Program for the Study of Retinal Degeneration was established in 1981 at the Eye, Ear, Nose and Throat Hospital headed by Dr. Nicolas G. Bazan. He has been actively involved in retinal research for over twenty years and is recognized as an expert in the field of retinal degenerative diseases and neurochemistry. A native Argentine, he moved to New Orleans in 1981, and in a very short time has established a state-of-the-art laboratory facility and assembled an outstanding team of scientists at the LSU Eye Center. While at LSU, Dr. Bazan has distinguished himself by his work on retinitis pigmentosa and on several fundamental issues of the biochemistry of the retina.

Grants from other institutions, particularly the National Eye Institute, National Institutes of Health, have strengthened the research funding of the program.



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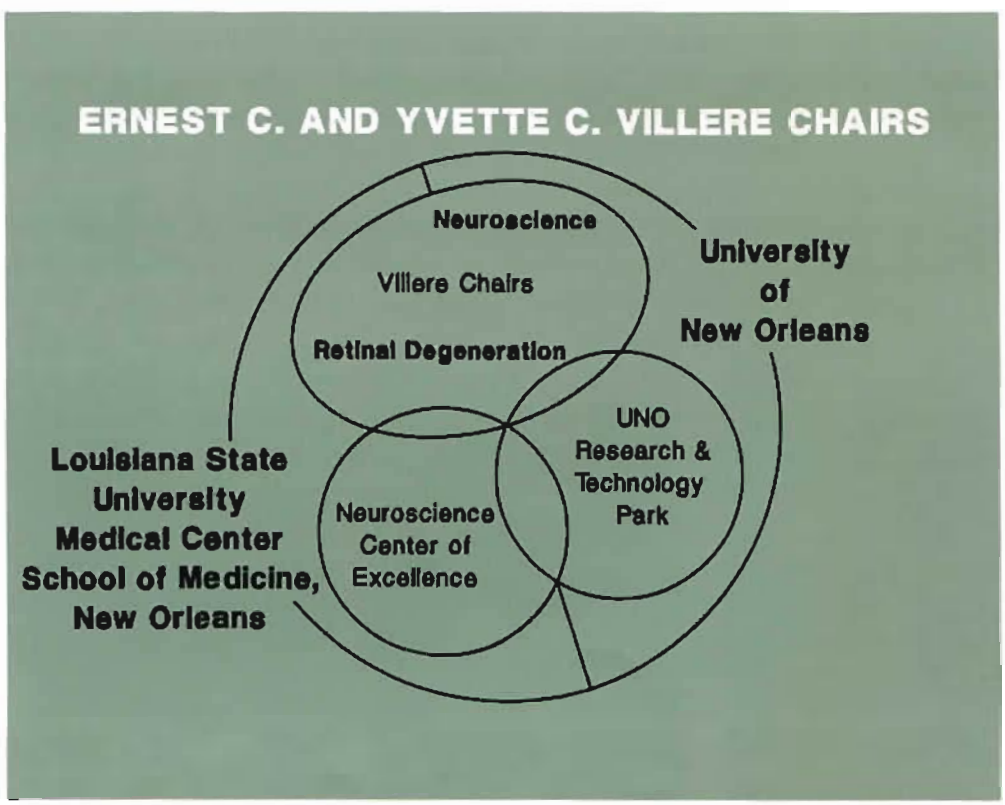


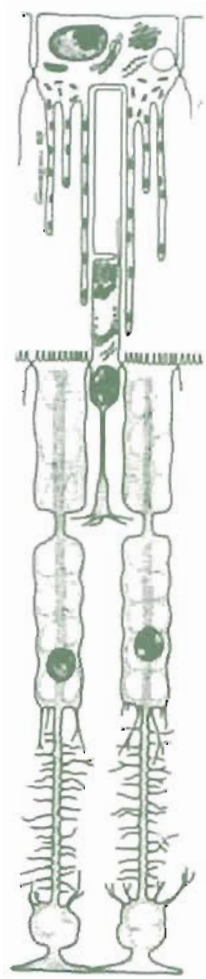
ACCOMPLISHMENTS TO DATE

Report of the Program

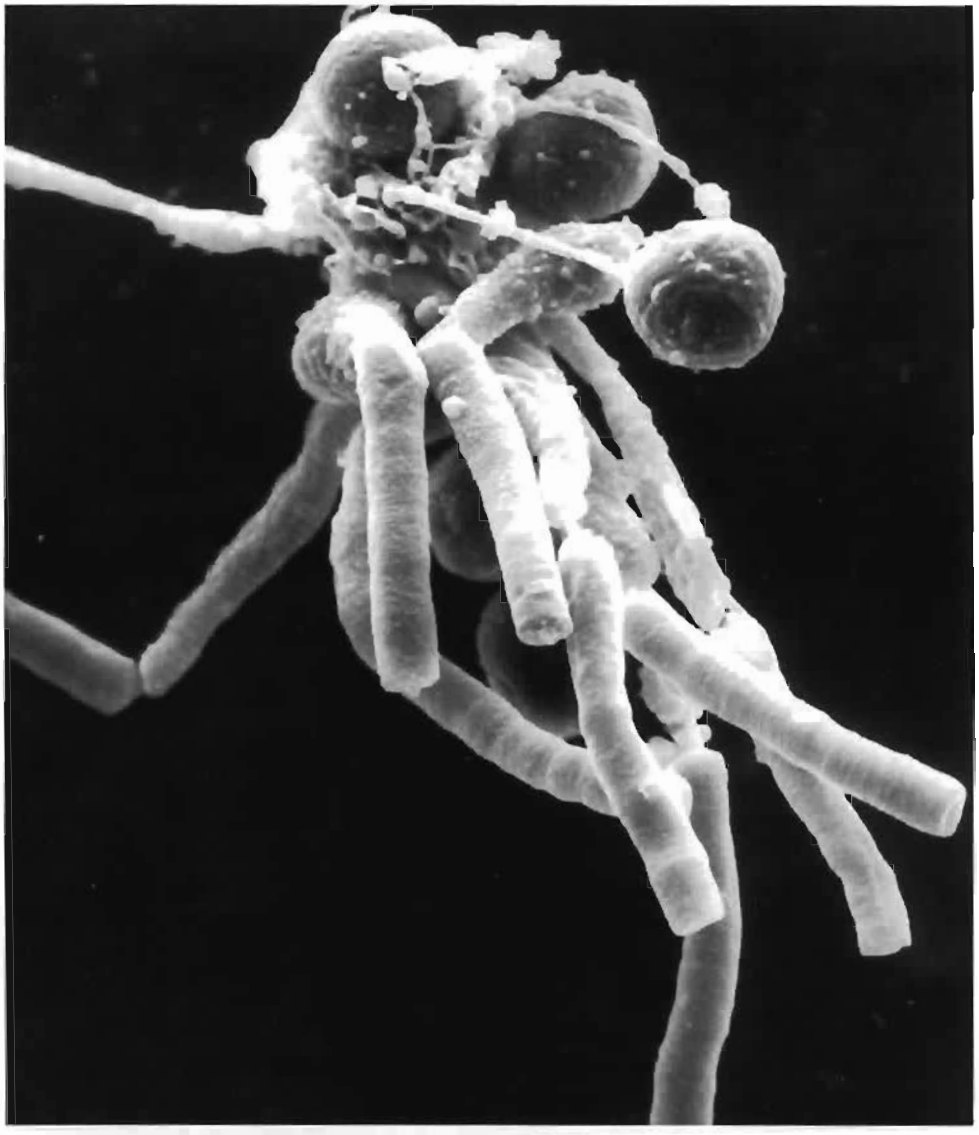
Today there are about 400,000 people in the United States affected by retinal degenerative diseases, and 3,000,000 worldwide. There currently exists no treatment to arrest or even to slow down the blinding consequences of retinal degeneration. Certain forms of these diseases, such as retinitis pigmentosa and Usher's syndrome, are inherited, while others occur as the result of aging, as in senile macular degeneration. Other conditions, for example, diabetic retinopathy, can also lead to blindness. Very little is presently known about the underlying abnormal mechanisms of these disorders. The major goal of the research conducted under the auspices of the Villere Chair is to study the metabolism and function of the retina in order to identify the alterations that lead to retinal degenerations such as retinitis pigmentosa. The research involves the use of biochemical, cell biological and molecular approaches to obtain insight into degeneration and regeneration. The knowledge emerging from this research represents the hope for the development of drugs and strategies for the treatment or prevention of the loss of sight in these patients.

In the past ten years sophisticated analytical capabilities were set up at the laboratories of the program including capillary gas-liquid chromatography, high-performance liquid chromatography, gas chromatography-mass spectrometry, thin-layer chromatography, and autoradiography, and access to both transmission and scanning electron microscopy. Twenty-six people are now working in the laboratories, including one full professor, two associate professors, one assistant professor, three instructors, five postdoctoral research fellows, one medical student, four research associates, three research assistants, three graduate students, and three administrative and editorial associates. Because Dr. Bazan recognized early the importance of a multidisciplinary approach, he has established collaborations with scientists both within and outside New Orleans.

Grants from other institutions have strengthened the research of the program. In particular, seven grants from the National Eye Institute have been awarded to Dr. Bazan in a ten-year period. Two of these grants will extend to 1992 and one of them provides support to 1996. Together these grants have brought several million dollars into the research on degenerative diseases of the eye. Dr. Bazan was also awarded the Program Development Award by the National Retinitis Pigmentosa Foundation, Inc., to help establish a clinical research program on retinal degeneration, and a large grant from the Schlieder Education Foundation to study membrane metabolism in inherited retinal degeneration. He has recently been named Senior Scientific Investigator by Research to Prevent Blindness, Inc., a recognition that carries support to start new projects. These funds have primarily been used to establish molecular biology and tissue culture as additional program research capabilities.



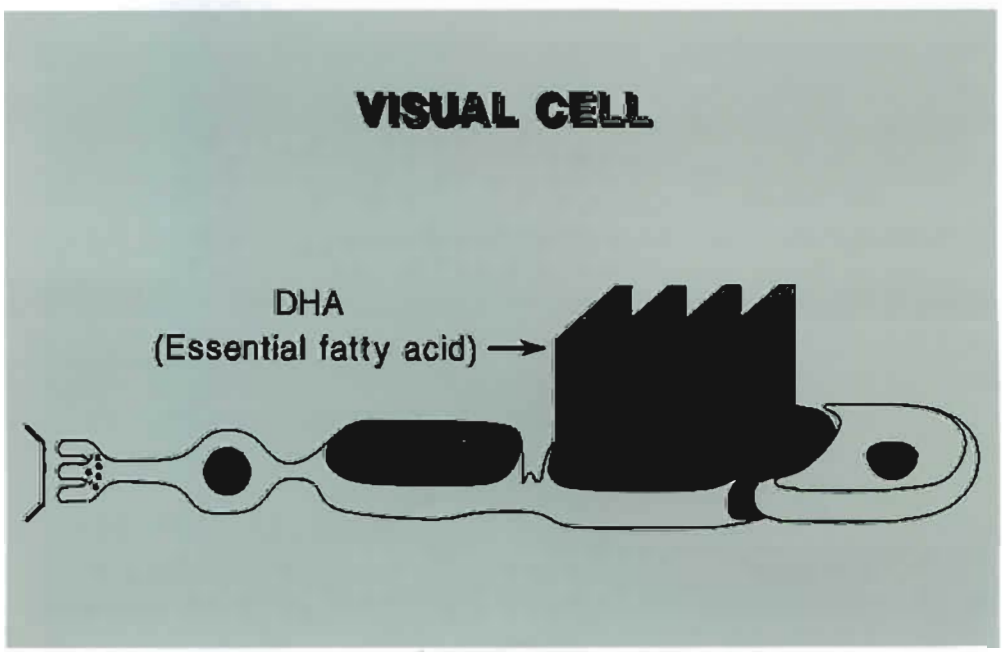
The scientific breakthrough of the identification of a biochemical defect in the blood of Usher's syndrome patients is but one example of the research advancements made by Dr. Bazan and his collaborators since he became the head of this program. Usher's syndrome, an autosomal recessive disorder, leads to blindness due to an inherited degeneration of the rod photoreceptor cells of the retina. Persons with these genes are born deaf and become blind early in life due to retinitis pigmentosa. This disease has special impact in Louisiana because of its relatively high incidence in the southeastern part of the State. The blindness of Usher's syndrome develops gradually, leaving many children with functional vision through their school years; nevertheless, whether the disease is diagnosed in infancy or in adulthood, nothing can be done to prevent or treat the ultimate loss of sight. The discovery of the biochemical alteration, which may be either the cause of or a consequence of Usher's syndrome, has opened many new avenues of research into retinal degeneration.



Group of isolated photoreceptor cells.

Research Collaborators

Christophe Baudouin	*Saint-Roch Hospital, Nice, France*
Elaine Berman	*Hadassah Hospital, Jerusalem, Israel*
Pierre Braquet	*Institut Henri Beaufour, Paris, France*
Gerald Chader	*National Eye Institute, Bethesda, MD*
William Connor	*University of Oregon Health Sciences Center, Portland, OR*
Lynette Feeney-Burns	*University of Missouri School of Medicine, Columbia, MO*
Pierre Gastaud	*Saint-Roch Hospital, Nice, France*
Carole Jelsema	*National Institutes of Health, Bethesda, MD*
Richard Lolley	*Veterans Administration Medical Center, Sepulveda, CA and University of California at Los Angeles, CA*
Jacques Mallet	*CNRS, Gif-sur-Yvette, France*
Martha Neuringer	*University of Oregon Health Sciences Center, Portland, OR*
Paul O'Brien	*National Eye Institute, Bethesda, MD*
M.Z. Pelias	*LSU Medical Center, New Orleans, LA*
Gholam Peyman	*LSU Eye Center, New Orleans, LA*
Jon Polansky	*University of California at San Francisco, CA*
Bo Siesjö	*University of Lund, Lund, Sweden*
Howard Sprecher	*University of Missouri School of Medicine, Columbia, MO*
Barbara Wiggert	*National Eye Institute, Bethesda, MD*



Research Synopsis

The research laboratories of the Villere Program have achieved the capacity and diversity to pursue several important scientific leads simultaneously. These major initiatives can be summarized as follows:

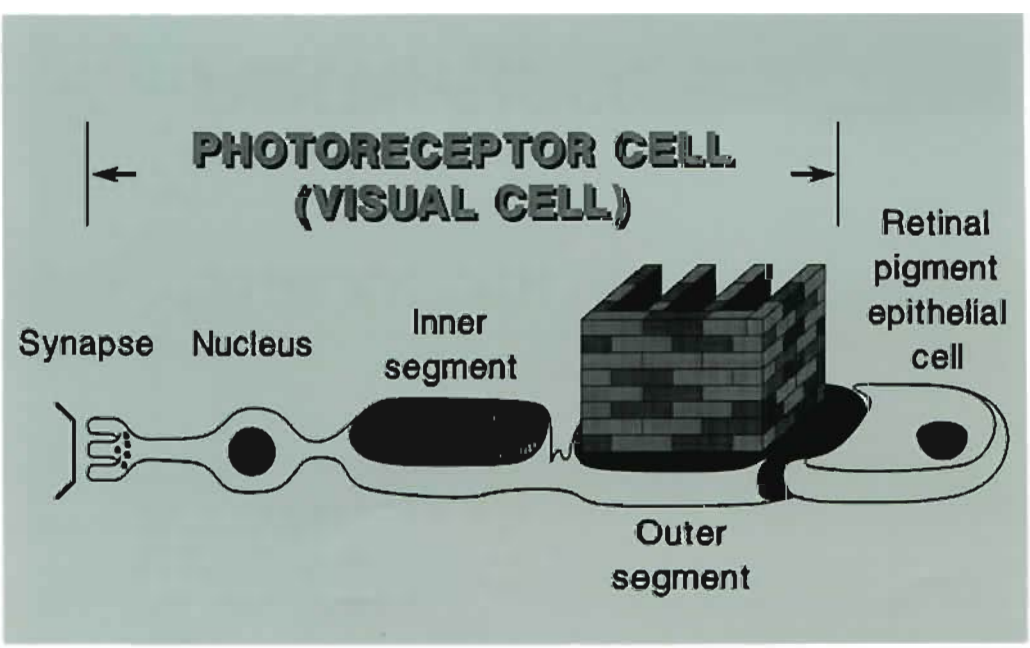
Large amounts of one fatty acid–DHA–are necessary for the retina's visual cells to function. The body does not produce this fatty acid. Dr. Bazan and his collaborators discovered that we get a piece of this fatty acid in our diets which our livers then enlarge to a usable form and subsequently shuttle to the retina. They also discovered that in the blood of patients with retinal degeneration there is a shortage of DHA. This finding led them to demonstrate a vital inter-organ connection that sustains retinal function. When this delivery system breaks down, as in retinal degenerative diseases, many of the essential building blocks of the visual cells are missing. These findings target a new area of drug research and development that may rebuild that important delivery system.

Research to understand the biological events that underlie the normal function of the retina: Almost half of the visual cell (photoreceptor) membranes are composed of lipids; in particular, docosahexaenoic acid (DHA) is especially prevalent and has been found to be more concentrated in the retina and synaptic membranes than in any other part of the body. Mammals must synthesize docosahexaenoic acid from precursor molecules in the diet such as linolenic acid; therefore it is an essential fatty acid family. The work of the Villere Program has focused on several aspects of docosahexaenoic acid metabolism, supply, and uptake in the eye to identify the role of these polyunsaturated fatty acids in the development, renewal, and function of visual cells. By using a combination of cell biological techniques, highly sensitive and specific biochemical procedures, and advanced analytical instrumentation, this research has contributed to an understanding of the role of docosahexaenoic acid in the eye.

Research to determine how cells of the retina communicate with each other: Recent research has uncovered new clues to the manner by which visual cells and adjacent pigment epithelial cells communicate with each other. Every morning the visual cells shed the posterior tips of the cells, and the adjacent pigment epithelial cells engulf these tips of the visual cells. Under normal conditions, the visual cells remain unchanged in size because, at the same time as shedding, new cell material is forming at the anterior ends of the visual cells. How both kinds of cells communicate to regulate this relationship is unknown. Dr. Bazan and collaborators have uncovered new signaling chemicals that allow one cell to "talk" to the other. When this line of communication fails, sight fails.

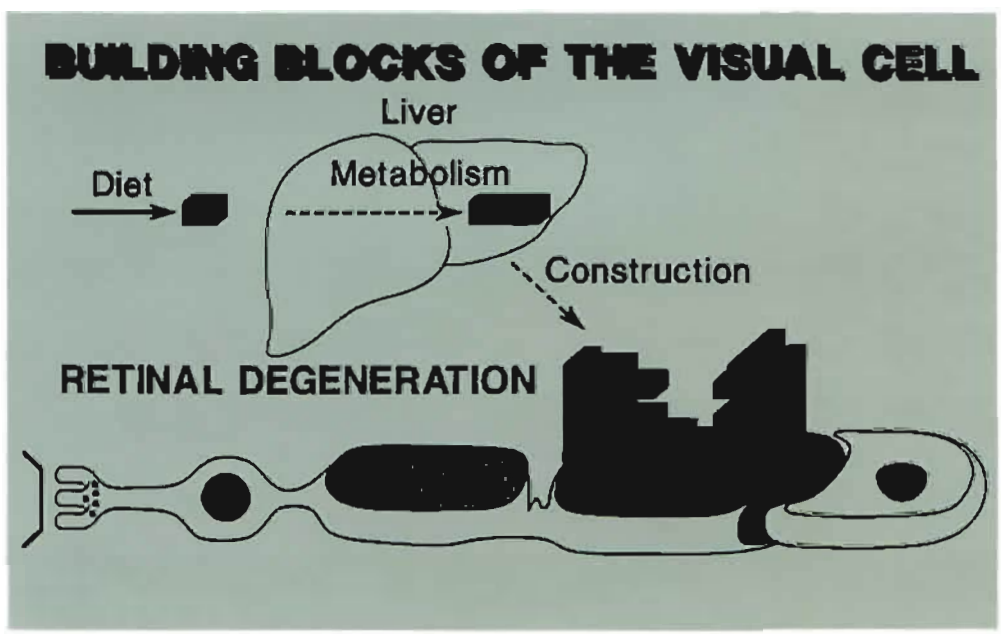
Research to define the biochemical steps that are altered in retinal degeneration: The goal of these investigations has been to pinpoint the biochemical pathways that are disrupted in retinal degenerations. Dr. Bazan's laboratory has been able to isolate the visual cells from an animal mutant with blindness and directly measure the phospholipids and fatty acids of the cells. Because a colony of control animals is also kept, the laboratory can compare and contrast the profiles of visual cells in mutants to those of healthy visual cells. It was found that visual cells from mutants had higher levels of saturated and monounsaturated fatty acids and lower levels of polyunsaturated fatty acids, such as docosahexaenoic and arachidonic acids, when compared to normal. These studies have established for the first time a deficit in the make up of the visual cells that correlates with blindness.

Research to identify the relationship between nutrition and the composition and dynamics of the retinal photoreceptors: One of the most exciting discoveries emerging from Dr. Bazan's research revolves around a particular protein molecule that proves effective in helping the visual cells retain the important polyunsaturated fatty acid, docosahexaenoic acid. It may be that retinal degeneration is in some way related to the loss of docosahexaenoic acid or to an inability of the retina to maintain its supply of this essential molecule. Ultimately, it is the goal of the research conducted by the Villere Chair that an increased understanding of the biochemical pathways of docosahexaenoic acid turnover will make possible the design of drugs to shift these pathways in order to slow down or prevent the progressive retinal damage associated with degenerative disorders.



The Villere Chair and the LSU Neuroscience Center of Excellence

Dr. Bazan's other research projects involve learning exactly how retinal cells talk to each other and to the other parts of the brain, the role nutrition plays in vision, and degeneration and regeneration of the brain itself. Even though the retina is closely associated with the eye, it is an integral part of the brain as well. It just faces outward as the mirror of man's soul. In 1991, the LSU Neuroscience Center of Excellence was funded by the state of Louisiana. As Director of the Neuroscience Center, Dr. Bazan continues his innovative research in the protection and regeneration of brain cells after injury from epilepsy, stroke and trauma. A team of basic and clinical investigators in many specialties will also expand research in neurodegenerative diseases such as ALS (Lou Gehrig's disease), Alzheimer's Disease, Parkinson's Disease, and others. The Neuroscience Center of Excellence is a direct outgrowth of the Ernest C. and Yvette C. Villere Retinal Degeneration Research Program. In addition, a second Ernest C. and Yvette C. Villere Chair for Neuroscience Research at the University of New Orleans will be funded later this year. Through the leadership of Chancellor Gregory O'Brien, Chancellor Perry Rigby and Dr. Nicolas Bazan, an interactive network of programs is being developed which includes the Villere Chairs, the LSU Neuroscience Center of Excellence, and the UNO Research & Technology Park. The collaboration of these complementary units will create a synergy greatly enhancing their success and their ability to conquer the last frontier of medicine–the brain.



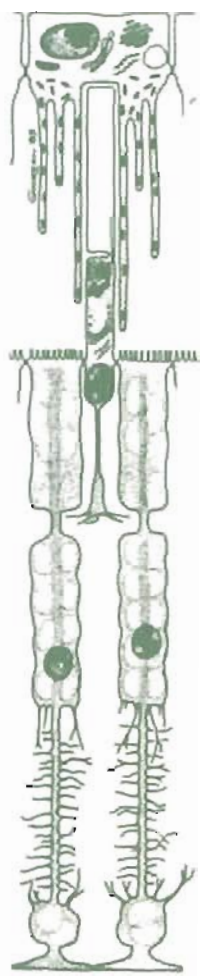
Technical Research Summary

Role of Polyunsaturated Fatty Acids in the Retina: Polyunsaturated fatty acids are involved in both the structure and function of the retina. They play a role in membrane fluidity, in the interaction of membrane lipids with proteins, and as the precursors of biologically active metabolites such as prostaglandins and leukotrienes. Arachidonic (20:4, n-6) and docosahexaenoic (22:6, n-3) acids are the major polyunsaturated fatty acids in the excitable membranes of photoreceptor cells and synapses. Arachidonic acid is also found in the lipids of all tissues; therefore, studies of arachidonic acid metabolism in nonneural tissues have created a foundation of information that has been used as a basis for studies in the retina and the brain. In the case of docosahexaenoic acid, peripheral tissues contain much smaller quantities of this fatty acid compared to the central nervous system.

Dietary deprivation of essential fatty acids for prolonged periods leads to drastic reductions in retina function.

In the newborn where the bulk of the formation of photoreceptor cells and synapses occurs, large requirements for DHA may be first met by the placenta and then by maternal milk. Linolenic acid, the precursor of DHA, is the most prevalent fatty acid of the n-3 series in the milk. In one research project, we used developing newborn mice as models for investigating the metabolism of DHA by studying the fate of injected, actively radiolabeled fatty acids. This work led to the discovery that the liver is a major source of this essential fatty acid for the formation of photoreceptor cells (in the retina) and synapses (in retina and brain). Further work supported by the Villere program led to the demonstration of two fundamental processes responsible for the maintenance of DHA in the central nervous system. First, a signaling mechanism may exist, through which the nervous system communicates to the liver the need for DHA, resulting in the secretion by the liver of a DHA-containing lipoprotein into the bloodstream. Although all organs are exposed to this DHA carrier, the central nervous system (retina and brain) takes up most of the DHA. The retina and/or retinal pigment epithelium and nervous tissue microvasculature may be endowed with a receptor-recognition mechanism which mediates the sequestering of DHA from the blood. Other tissues may express only a small number of such receptors and hence are capable of retaining smaller amounts of DHA than the central nervous system.

Visual cells renew their outer segment membranes daily through a bipolar process consisting of shedding of outer segment tips and membrane biogenesis at the outer segment base. These two processes combine to maintain outer segment length. Shedding of outer segment membranes occurs simultaneously with phagocytosis by the retinal pigment cells. Despite this daily turnover of their membranes, visual cells avidly retain DHA.



Work supported by the Villere Program led also to a new understanding of DHA in rod outer segment renewal. This work shows that DHA builds photoreceptors in two ways: 1) by a process of molecular replacement producing an overall diffuse appearance and; 2) by a continuous protein-associated pathway from the rod inner segment that produces enriched patches of membranes and matches the rate of disc synthesis.

A DHA-retrieval mechanism analogous to the liver-blood transport system may also operate in the interphotoreceptor matrix. Here, the major protein, interphotoreceptor retinoid binding protein, and other matrix components have been shown to contain endogenous DHA, suggesting that they may serve as intercellular transporters for fatty acid retrieval by visual cells. The molecular basis of the metabolic handling of essential fatty acids likely involves: 1) intercellular retrieval mechanisms through fatty acid binding proteins; 2) rapid formation of thiol esters by activating enzymes that trap DHA intracellularly; and 3) interorgan delivery through blood lipoproteins.

Identification of Biochemical Alterations Early in the Differentiation of Visual Cells in Inherited Retinal Degeneration: Rod photoreceptors of the retina develop and differentiate during the first two weeks after birth. In the inherited retinal degeneration of *rd* mutant mice, developing photoreceptor cells degenerate before they reach maturity. This degeneration can be detected at approximately day 12 after birth.

In this study, we applied capillary gas-liquid chromatography to the analysis of individual phospholipid classes in photoreceptor cells dissociated from normal and *rd* mouse retinas at different ages of postnatal development. Our compositional studies of photoreceptor cells have focused upon two ages: 5-6 days, prior to onset of rod outer segment disk membrane formation; 10-13 days, after rod outer segments have reached their mature length, and the photoreceptors are fully developed. We found that the total phospholipid content and mole percent distribution of individual phospholipid classes in immature *rd* photoreceptors were similar to values for normal cells. We documented that, concomitant with the onset of outer segment biogenesis, normal photoreceptor cells undergo a dramatic increase in the accumulation of DHA. In contrast, the content of another important polyunsaturated fatty acid, arachidonic acid, remains fairly stable during development. We found that the amounts of saturated fatty acids such as myristate and palmitate and of monounsaturated fatty acids such as oleate decrease in normal cells.

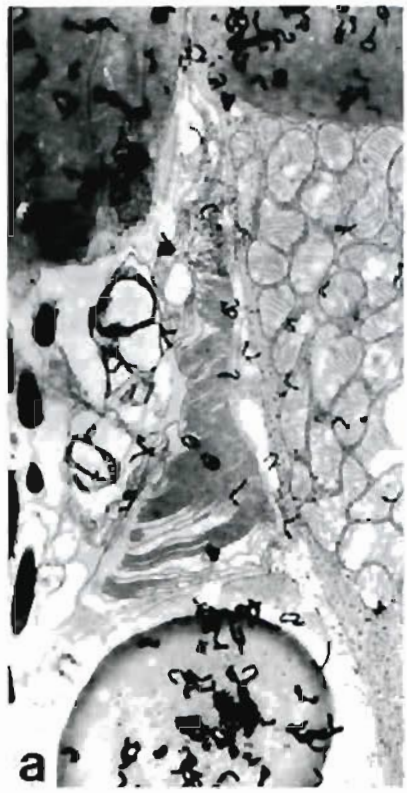
These studies shows that immature *rd* photoreceptors may be retarded in the development of lipid metabolism and that fatty acid metabolism is altered by expression of the *rd* gene or by the associated impairment of photoreceptor cell differentiation.

To establish whether early defects in DHA metabolism are due to alterations in the biosynthesis of DHA (or in its packaging into lipoproteins), or perhaps to alterations in the transport from the liver to the photoreceptors or within the photoreceptors themselves, several further studies were conducted. These studies shows that early defects in DHA metabolism may be due to alterations in transport from the liver to the photoreceptors or to alterations within the photoreceptors, and not in the synthesis of DHA.

Studies Aimed at Determining Therapeutic Approaches for Retinal Degenerative Diseases: In retinitis pigmentosa variably progressive visual loss due to retinal photoreceptor deterioration takes place. With the aim of gaining insight into possible

agents that might retard or stop the deterioration, the first clinical study of a possible new treatment in humans was conducted by the Villere Program by administering ganglioside GM_1 in a prospective, double-blind, randomized, placebo-controlled trial in 30 persons with retinitis pigmentosa with or without congenital deafness. In comparing baseline performance on the two principal study outcomes, visual field area and electroretinographic response amplitudes, a marginally statistically significant increase in visual field area in the ganglioside-treated group was found. The subgroup of subjects who had recordable electroretinograms at baseline and who received the drug showed an increase in amplitude to all stimuli in three of five cases. The results are encouraging and suggest that further studies of the possible benefits of ganglioside administration to retinitis pigmentosa patients are warranted.

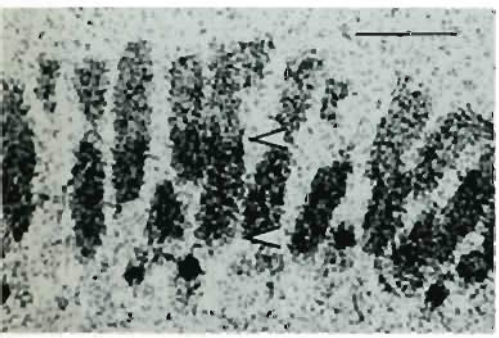
Usher's syndrome is an autosomal recessive disorder that leads to blindness due to degeneration of the rod photoreceptor cells. A study of the fatty acid composition of plasma phospholipids and triacylglycerols from Usher's syndrome patients has led to the discovery that there is a decreased content of docosahexaenoate and arachidonate of plasma phospholipids. The major finding from this study is that plasma phospholipids from Usher's syndrome patients contain significantly less docosahexaenoate and arachidonate than controls. It has been found that in triacylglycerols, there are no differences in either the total fatty acid content or the levels of individual fatty acyl groups between control and affected individuals. However, plasma phospholipids in Usher's patients contain 70% of control levels of arachidonate and 64% of control levels of docosahexaenoate. While plasma triacylglycerols are directly related to energy metabolism and to fat absorption through the gastrointestinal tract, phospholipids represent to a large extent molecules, comprising lipoproteins, being transported through the bloodstream. The lowered level of docosahexaenoate and arachidonate in plasma phospholipids of Usher's patients may reflect an altered metabolism of these lipids by affected individuals. The reported changes may reflect alterations in polyunsaturated fatty acid metabolism that may be involved in the pathogenesis of the disease.



Electron microscopy shows dark trails that mark the location of the fatty acid, DHA, in a single cone photoreceptor cell.

Oxygenated Products of Arachidonic and Docosahexaenoic Acids: Eicosanoids are oxygenated products of arachidonic acid with very powerful biological effects. Prostaglandins (PGs) are synthesized by cyclooxygenase; hydroxyeicosatetraenoic acids (HETEs) and leukotrienes (LTs) are synthesized by lipoxygenase. These compounds act as mediators and modulators of inflammation by influencing chemotaxis, phagocytosis, and lysosomal enzyme release. They have potent vascular effects, causing vasodilation, vasoconstriction, changes in capillary permeability, and platelet aggregation. Prostaglandins are important mediators of thermoregulation, gastric acid secretion, and various aspects of the reproductive cycle. Leukotrienes are extremely potent bronchoconstrictors and are mediators of asthma and anaphylaxis. There is increasing evidence that eicosanoids are modulators of central and peripheral neurotransmission.

As mentioned earlier, the physiological significance of docosahexaenoic acid in the retina is not clearly understood. For this reason, studies were conducted to explore the possibility that oxygenated metabolites may arise from this fatty acid. Analogous to biologically active metabolites of the n-6 fatty acid, arachidonic acid, which synthesizes eicosanoids, DHA may lead to the synthesis of docosanoids in the retina. In fact the retina was found to be able to make lipoxygenase reaction products. Indeed, a correlation was also found between retinal degeneration and alterations in the capacity to synthesize docosanoids in the retina and retinal pigment epithelium.



Autoradiography shows accumulation of the fatty acid building blocks in the visual cells.

Messengers in the Retina: Excitable membranes, with specialized presynaptic and postsynaptic domains, represent a large surface area in nervous tissue, including the retina. The role of membrane fatty acids in neurotransmitter release and action is not fully understood. In the postsynaptic membrane, target responses are specified initially by interaction with receptors at the outer leaflet, coupled to transducer proteins that provide a link with a chain of chemical events leading to the physiological actions on the postsynaptic neuron and then in circuits of neurons. The physiological significance of excitable membrane phospholipids is not well understood. There is currently being generated, however, a profusion of information on inositol lipids and cell signaling.

The retina upon K^+ depolarization activates the synthesis of prostaglandins (PGs) and hydroxyeicosatetra-(5,8,11,14)-enoic acids (HETEs).

In a continuing study of the metabolism of arachidonic acid in the retina, evidence was obtained that short-term exposure to light increases synthesis of HETE and prostaglandin D2 (PGD2) and stimulates the uptake and metabolism of arachidonic acid in phospholipids and triacylglycerols in rat retina. In the light-exposed groups there was a large increase in the conversion of arachidonic acid to leukotriene B_4, 5-HETE, 15-HETE, and PGD_2. The peroxidation of arachidonic acid in isolated rod outer segments was also studied. There was more oxidation of arachidonic acid in light-exposed rod outer segments, as compared to rod outer segments incubated in the dark. Vitamin E and nordihydroguaiaretic acid inhibited the light-induced formation of some of these products. The data indicate that photooxidation of arachidonic acid in rod outer segments is accompanied by enzymatic oxidation that is stimulated by light.

The process of photoreceptor shedding is continuous and complex and involves the neural retina, the visual cells (the rods and cones), and the retinal pigment epithelium. The process is triggered by light and is dependent on a dark phase. Although the histological characteristics of photoreceptor shedding have been studied extensively, the biochemical mechanisms behind this process are not defined. The basic steps in the shedding process are 1) detachment of the outer segment disks; 2) recognition and attachment of shed disks to the retinal pigment epithelium; 3) internalization of the disks by the retinal pigment epithelium; 4) fusion of the disks with lysosomes to form the phagosome; and 5) digestion of the disk components. It is not clear whether disks detach due to a signal from the retina or if disks are broken off by the retinal pigment epithelium. The signals involved in these processes are not defined.

Products of the 5-lipoxygenase-mediated oxygenation of arachidonic acid, the leukotrienes, are well-known to be important mediators of the phagocytic processes. The possibility that leukotrienes are involved in the phagocytosis of shed disks by the retinal pigment epithelium was explored under the auspices of the Villere Program. Levels of LTC_4 were stimulated 5 minutes after light onset (prior to detectable shedding) and declined below dark levels as shedding progressed. These data suggest a correlation between 5-lipoxygenase activity and the events of photoreceptor shedding and phagocytosis.

Also demonstrated was the capability of the retina and retinal pigment epithelium for synthesis of leukotrienes and other eicosanoids. It has been shown that there is indeed an active leukotriene accumulation in isolated rod outer segments.

Methodology: The development of suitable analytical techniques and methodology applicable to the study of fatty acid composition of phospholipids and to the isolation and identification of oxygenated metabolites of arachidonic and docosahexaenoic acids, in particular, was a prerequisite to the research described in the previous sections.

A methodological problem that has been encountered in the past is the normal phase high-performance liquid chromatography (HPLC) of hydroxylated products of docosahexaenoic and arachidonic acids. Diacylglycerols present in lipid extracts of rat retina coelute with monohydroxy derivatives of docosahexaenoic and arachidonic acid. This coelution of diacylglycerols with monohydroxypolyunsaturated fatty acids can lead to a significant error in estimation of lipoxygenation activity by conversion of radiolabeled precursors, because the incorporation of fatty acids into diacylglycerols is very active in many tissues. We have developed an alternative extraction scheme and reverse-phase HPLC procedures that result in the complete separation of hydroxy fatty acids and diacylglycerols.

High-performance liquid chromatography (HPLC) offers several advantages over analysis of fatty acids and eicosanoids by the alternative techniques, gas-liquid chromatography (GLC) and thin-layer chromatography (TLC).

HPLC provides a convenient method for the purification and collection of fatty acids and eicosanoids because it is a nondestructive technique. HPLC has much greater resolving power than TLC and the recovery of compounds by the collection of HPLC eluent is much simpler and more efficient than recovery from a TLC plate, which requires scraping the silica gel and eluting the compounds from the scrapings. Quantitation of labeled metabolites can be done very conveniently by on-line flow scintillation detection. HPLC is also a necessary and efficient cleanup procedure used prior to the quantitative or qualitative analysis of eicosanoids by gas chromatography-mass spectrometry.

Oxygenated metabolites of arachidonic and docosahexaenoic acids, the eicosanoids and docosanoids, are produced in extremely small quantities in any given tissue; therefore, qualitative and quantitative analyses present an important challenge. The major problems in such analyses involve extraction of the compounds of interest, with appropriate removal of water-soluble contaminants and interfering lipids, and separation of the various classes of eicosanoids, the chemically similar isomers and derivatives, and the docosanoids. Some breakthroughs and advances in these procedures have already been mentioned. Aside from problems of quantitative extraction and isolation, the rapid postmortem stimulation of eicosanoid synthesis has confounded the results of many studies. The technique of head-focused microwave radiation has reduced the complications arising from postmortem effects. Because of the potential therapeutic importance of manipulation of the arachidonic acid cascade in cerebral ischemia, stroke and edema, epilepsy, and aging disorders, and future possible uses of oxygenated products of docosahexaenoic acid, we are continuing our efforts to refine our methodology.

During the past years the laboratories of the Villere Program have expanded their cell biology facilities, including equipment for molecular biological investigation of the expression of individual genes. Also microscopic methods were expanded, including autoradiography, which is capable of indicating the precise cellular location of radioactive tracer molecules applied to the retina. Improved tissue culture facilities have permitted the maintenance of highly specialized cell lines for studies on retinal degeneration mutants.

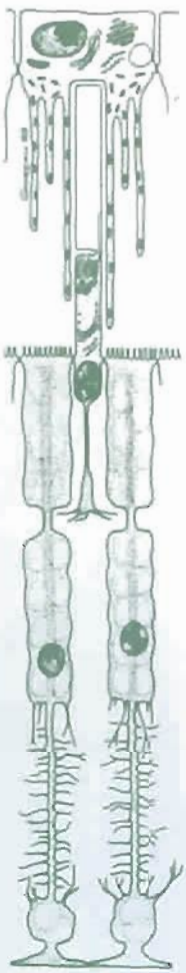
BIOGRAPHICAL SKETCH

First Ernest C. and Yvette C. Villere Professor of Ophthalmology

Nicolas G. Bazan, M.D., Ph.D., is the Director of the Louisiana State University Neuroscience Center of Excellence and Ernest C. and Yvette C. Villere Professor of Ophthalmology, Biochemistry and Molecular Biology and Neurology at LSU Medical Center School of Medicine, New Orleans.

Dr. Bazan received his M.D. and D.Med. Sci from the Facultad de Medicina, Universidad de Tucuman, Argentina.

Dr. Bazan is a member of the Neurosciences and Behavior Study Section, Division of Research Grants. He has served on several federal advisory committees of the National Institutes of Health. He is a member of the Scientific Advisory Board of the Giovanni Lorenzini Medical Research Foundation. He has been involved with organization, advisory boards and chairmanships of several major symposiums in this field including the "Brain 91" symposium satellite on neurotransmitters in brain injury (Key West, Florida). He lectures extensively and is internationally recognized for his expertise in brain injury, stroke, basic mechanisms of epilepsy, lipid second messengers and retinal degeneration. He is the recipient of a Jacob Javits Neuroscience Investigator Award from the National Institute of Neurological Disorders and Stroke. He is the author of several highly quoted landmark papers such as the one that was chosen to be a Citation Classic in Current Contents (***30:***10, 1991).



He is active in several faculty service positions at LSU including the co-direction of the Neuroscience Training Program. Dr. Bazan has published over 220 papers in refereed journals, 350 abstracts, over 100 reviews and book chapters and has edited 13 books. He currently serves on the program committee of the American Society of Neurochemistry and International Society of Neurochemistry. He is a Council member of the International Society for Pathophysiology, member of the International Advisory Board of the International Conference of Prostaglandins and Related Compounds, member of the organizing committee of the Ocular Cell and Molecular Biology conference and a member of the International Advisory Committee of the International Symposium on Retinal Degeneration.

Dr. Bazan and Dr. David U'Prichard of Johns Hopkins University founded *Molecular Neurobiology*, a journal providing up-to-date reviews of hot topics regarding function and diseases of the nervous system. Advances in pathogenesis and therapeutics of retinal degenerative diseases as well as other disorders affecting the nervous system are covered by *Molecular Neurobiology*.

The recognition of Dr. Bazan's activities is reflected in invitations to major international meetings to speak about the work conducted under the auspices of the Chair.

Dr. Bazan has been an invited speaker at the international conferences on retinal degenerations held in Alicante, Spain (1984), Sendai, Japan (1986), San Francisco (1988) and Stockholm, Sweden (1990). These conferences gather scientists and clinicians working on retinal degenerations from all over the world to present their latest findings. The meetings provide an unusual opportunity to discuss research results, exchange information and ideas, establish collaborations with other scientists, and define new leads to advance our understanding of retinal degenerations, with the aim of developing effective treatments.

These invited lectures have been published as chapters in the books emerging from each of these conferences, for worldwide distribution. Those chapters and books are:

- Bazan NG, Birkle DL, Reddy TS: Biochemical and nutritional aspects of the metabolism of polyunsaturated fatty acids and phospholipids in experimental models of retinal degeneration. In *Retinal Degeneration: Experimental and Clinical Studies*, MM LaVail, G Anderson, J Hollyfield (eds), Alan R. Liss, Inc., New York, pp 159-187, 1985.
- Bazan NG, Scott BL: Docosahexaenoic acid metabolism and inherited retinal degeneration. In *Degenerative Retinal Disorders: Clinical and Laboratory Investigations*, JG Hollyfield, RE Anderson, MM Lavail (eds), Alan R. Liss, New York, pp 103-118, 1987.
- Bazan NG: The identification of a new biochemical alteration early in the differentiation of visual cells in inherited retinal degeneration. In *Inherited and Environmentally Induced Retinal Degenerations*, Alan R. Liss, New York, pp 191-215, 1989.
- Bazan NG, Rodriguez de Turco EB, Gordon WC: Docosahexaenoic acid and phospholipid metabolism in photoreceptor cells and in retinal degeneration. In *Retinal Degenerations*, Chapter 14, RE Anderson, JG Hollyfield, MM LaVail (eds), CRC Press, Boca Raton, Florida, pp. 151-165, 1991.

In September of 1992 the Fourth International Congress of this series will be held. Dr. Bazan has been ask to present a lecture on retinitis pigmentosa and to join the international advisory board that oversees the scientific organization of the event.

Dr. Bazan's research has been subjected to intense peer review at the national level on each of the several occasions that he submitted grant proposals for the initiation and extension of research programs. The following are his funded grants from the National Eye Institute, National Institutes of Health, United States Public Health Service:

- Biosynthesis of Phosphatidic Acid in the Retina, pilot project, 1981-1982 ($15,000).
- Role of Lipids in Retinal Degenerative Diseases, 1982-1986 ($287,516).
- Prostaglandins and Lipoxygenase Metabolites in Retina, 1984-1987 ($232,911).
- Docosahexaenoic Acid Metabolism in Retina, 1987-1992 ($497,537).
- Role of Docosahexaenoic Acid Metabolism in Retina, 1992-1997 ($1,278,988).
- Leukotrienes and Prostaglandins in Photoreceptor Renewal, 1987-1992 ($576,552).
- Leukotrienes and Messengers in Photoreceptor Renewal, 1992-1997 ($508,000).

Since the retina is an integral part of the central nervous system, much can also be gained by study of the brain. Thus complementary studies on brain are supported by a grant from the National Institute on Neurological and Communicative Diseases and Stroke, National Institutes of Health, United States Public Health Service. These projects explore important problems of the brain and neurology and at the same time

provide a unique depth and breadth to the overall neurobiological research activities of the Chair's laboratories. This grant is:

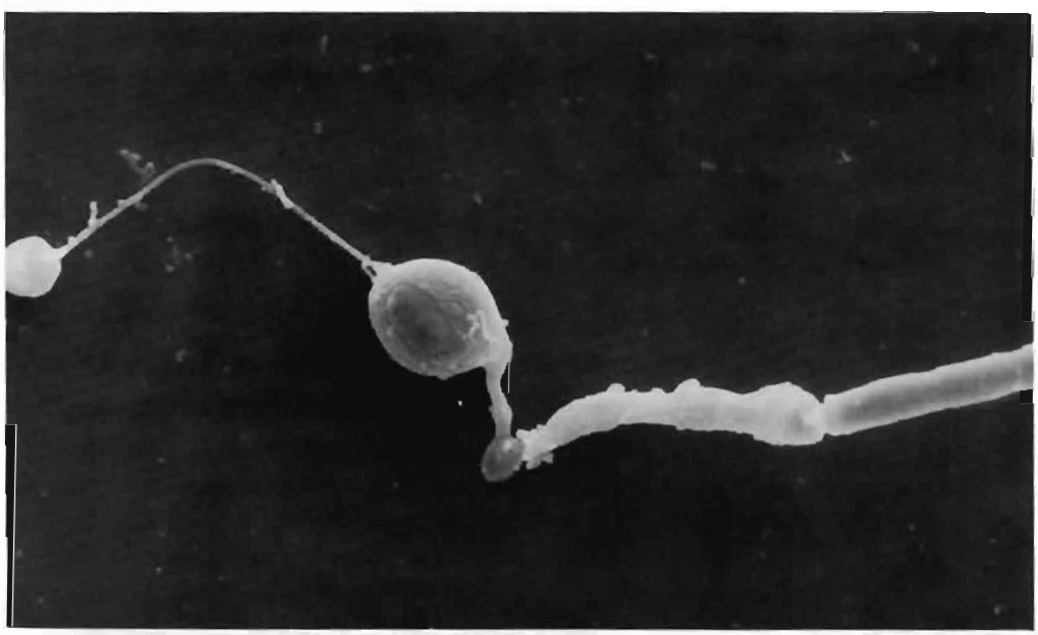
- Role of Phospholipids and Arachidonic Acid in Epilepsy, 1986-1996 ($1,302,887).

Dr. Bazan's research has also been acknowledged several times by awards of a competitive nature from other agencies or associations:

- March of Dimes, 1982-1983 ($7,000).
- Research to Prevent Blindness, 1982-1983 ($35,000).
- Fight for Sight, 1982-1983 ($9,000).
- William and Mary Greve Award, 1984 ($35,000).
- Baton Rouge Evening Lions Club, 1984-1985 ($25,000).
- National Retinitis Pigmentosa Foundation, Inc., Program Development Award, 1984-1986 ($70,000).
- American Diabetes Association, 1984-1986 ($50,000).
- Edward G. Schlieder Educational Foundation Award, 1986-1989 ($99,000).
- Research to Prevent Blindness Senior Scientific Investigator, 1988-1989 ($40,000).
- Glaxo Research Laboratories, 1989-1990 ($900,000)

Dr. Bazan was invited to join the editorial boards of the following prestigious scientific publications:

Journal of Neurochemistry, 1981-1989.
Neurochemical Pathology, 1983-; co-founder.
Journal of Neuroscience Research, 1985-.
Neurochemical Research, 1986-.
Molecular Neurobiology, 1987-; editor-founder.
Journal of Lipid Mediators, 1988-; associate editor-founder.
Journal of Cerebral Blood Flow and Metabolism, 1988-.
Journal of Molecular Neuroscience, 1989-.
Journal of Nutritional Biochemistry, 1990-; co-founder.



Isolated photoreceptor cell (visual cells).

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3. Giusto NM, Bazan NG. (1982) Highly active phosphatic acid pool in microsomal and photoreceptor membranes of vertebrate retinas. Suppl Invest Ophthalmol Vis Sci 22:183.

4. Giusto NM, Ilincheta de Boschero MG, Bazan NG. (1982) Phosphatidic acid in photoreceptor membranes. 5th Int Congress of Eye Res, Nijmegan, The Netherlands.

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7. Giusto NM, Bazan NG. (1983) Accumulation of fatty acid methyl esters in anoxic retina and brain. 14th Annual Meeting, ASN, Honolulu, Hawaii, 14:104.

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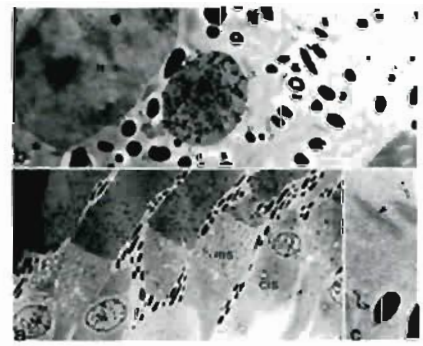
15. Birkle DL, Bazan NG. (1983) Synthesis of prostaglandins and related eicosanoids in the mammalian retina. Int Symp on Physiological Role of Phospholipids in the Nervous System. Harrison Hot Springs, B.C., Canada.



Dark spots show where the fatty acid "bricks" accumulate in the visual cells as seen by the electromicroscope.

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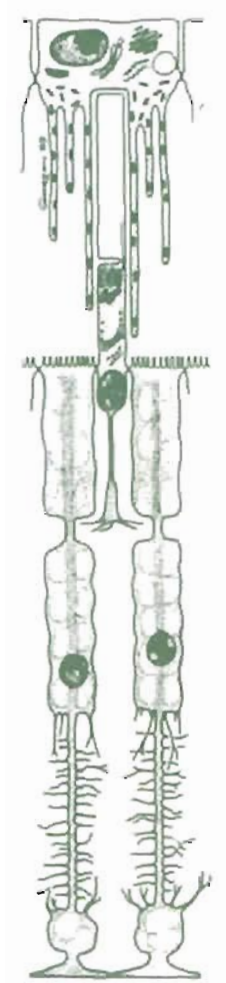

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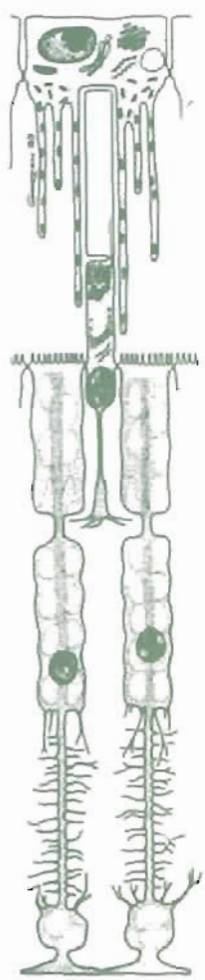

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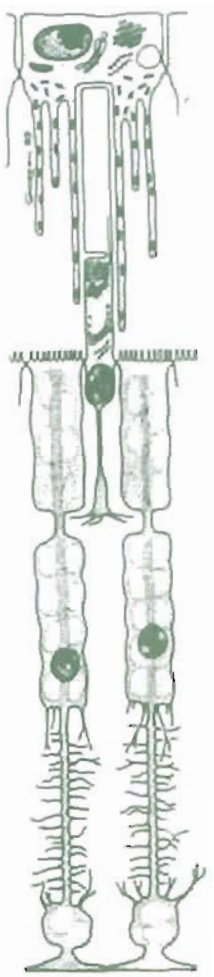

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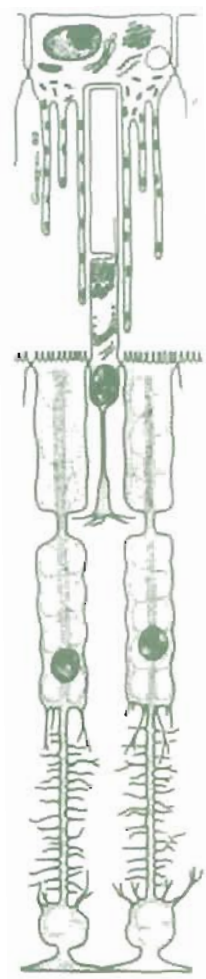

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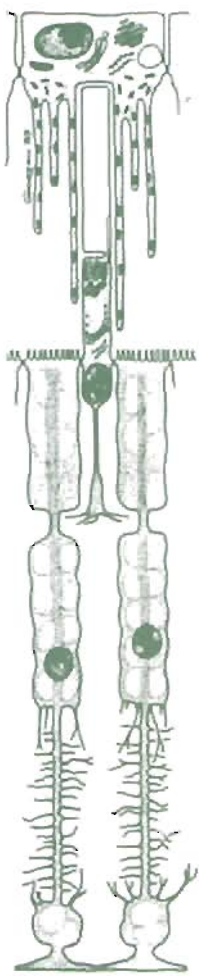

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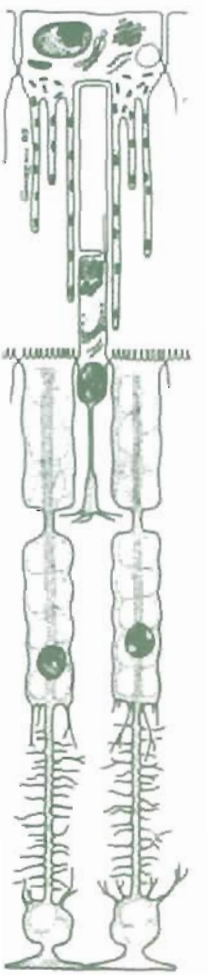

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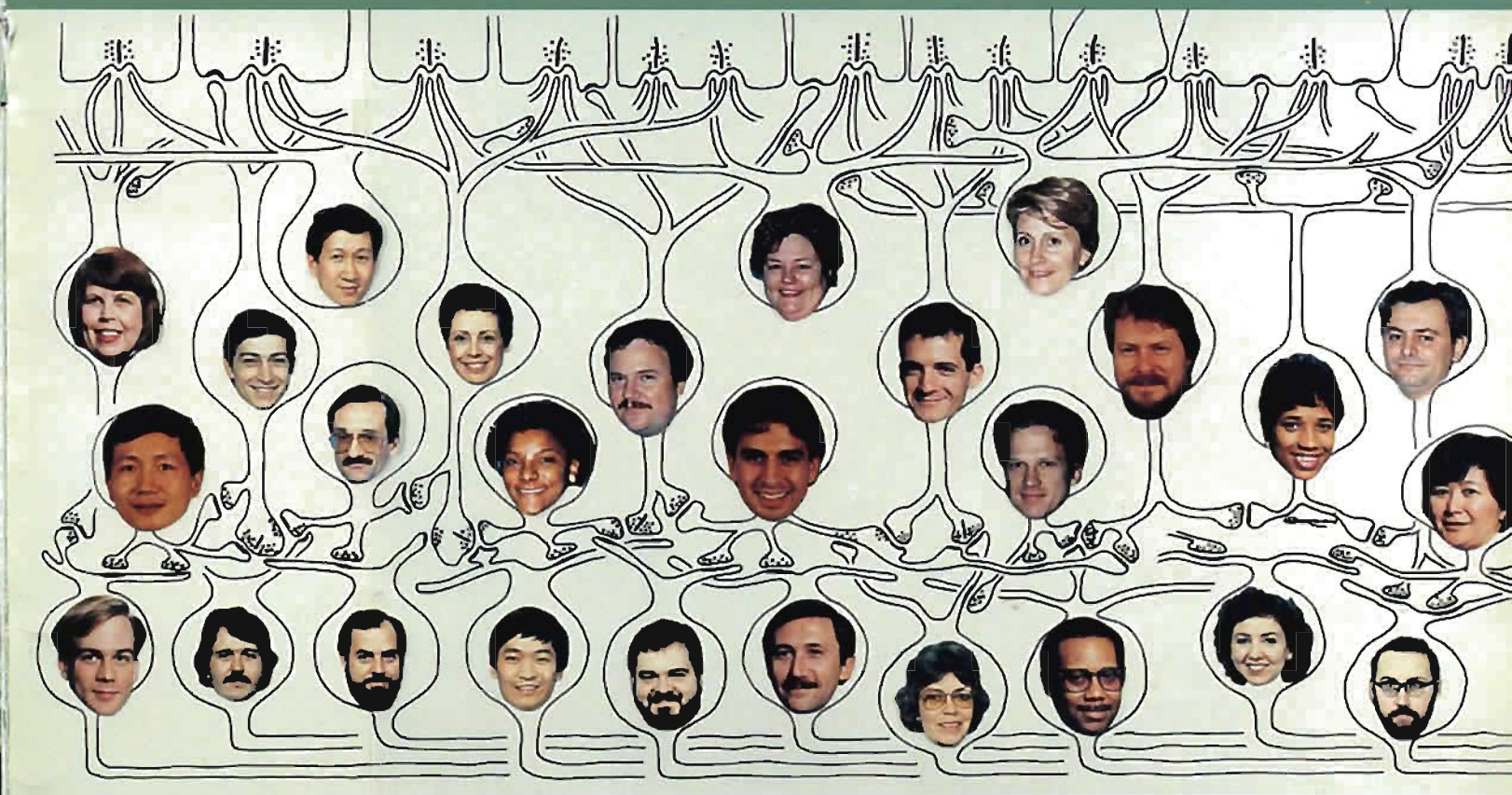

The Ernest C. and Yvette C. Villere Program Team

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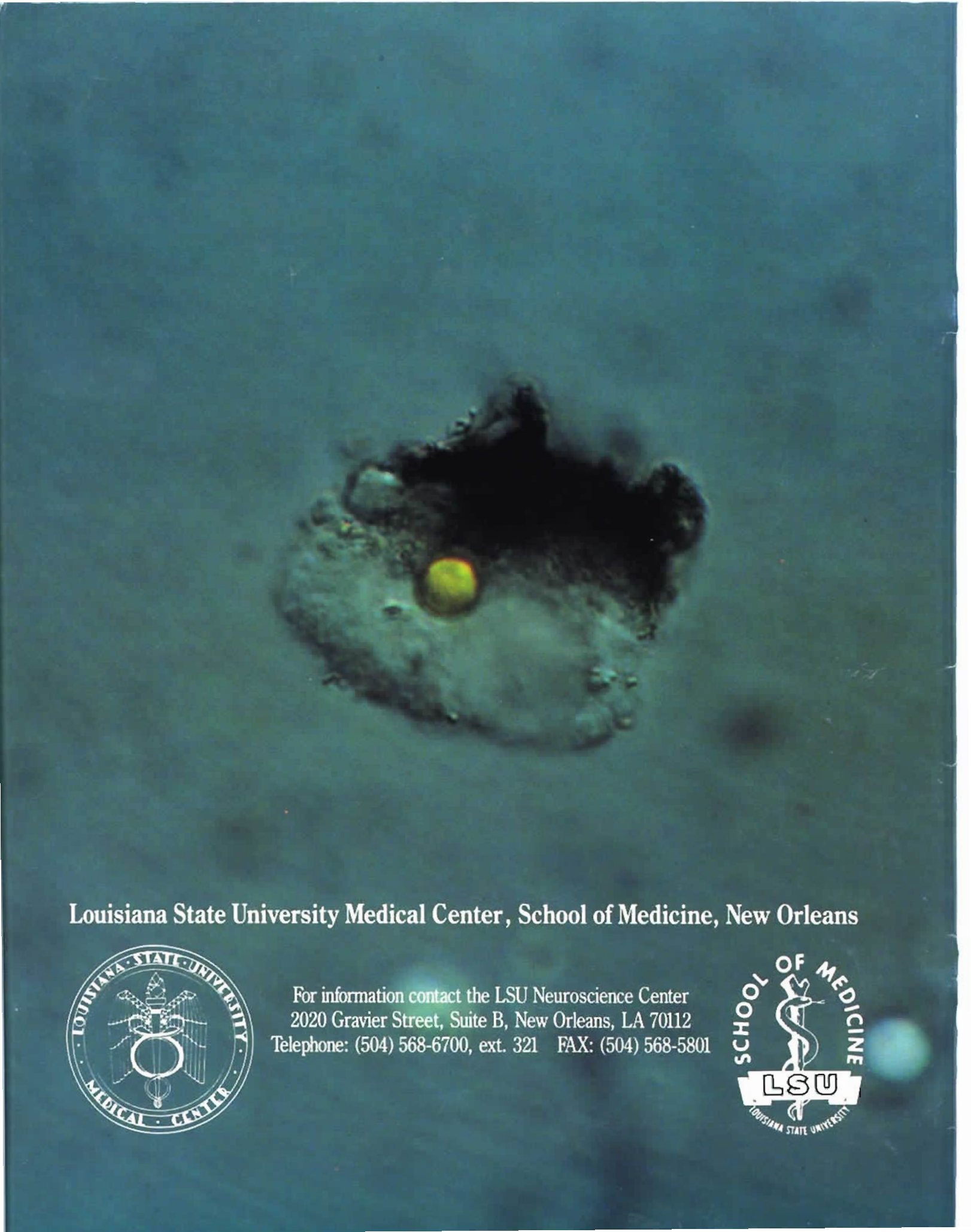

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