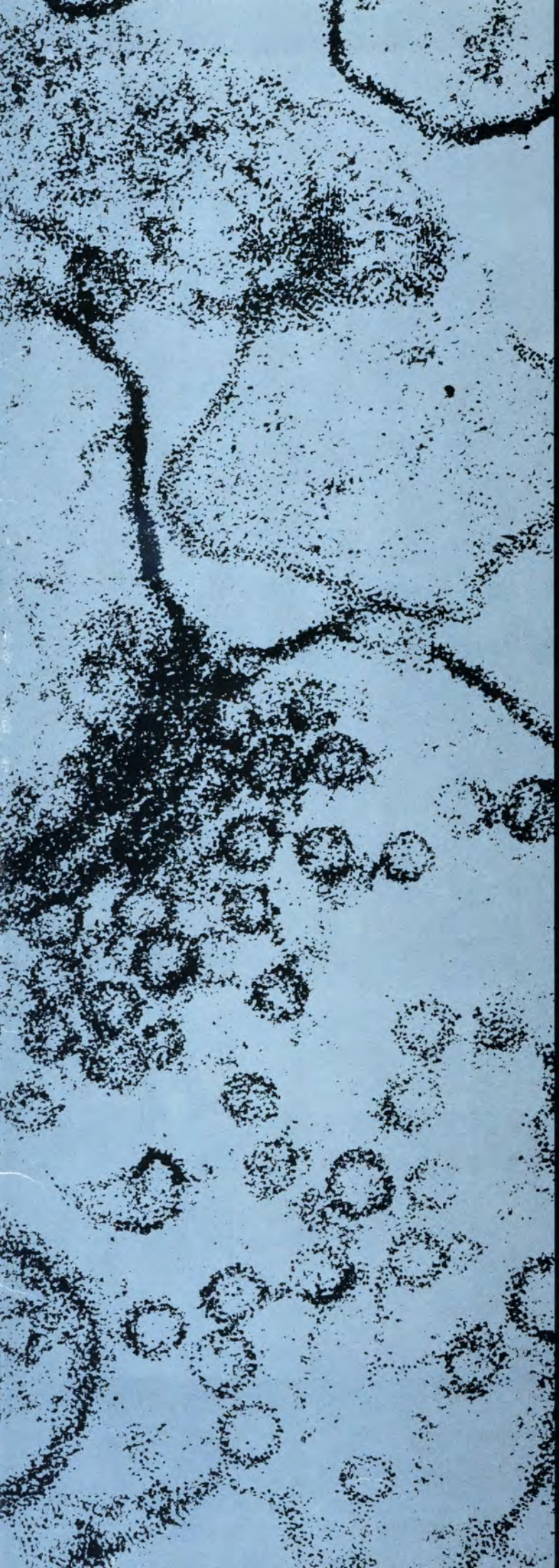
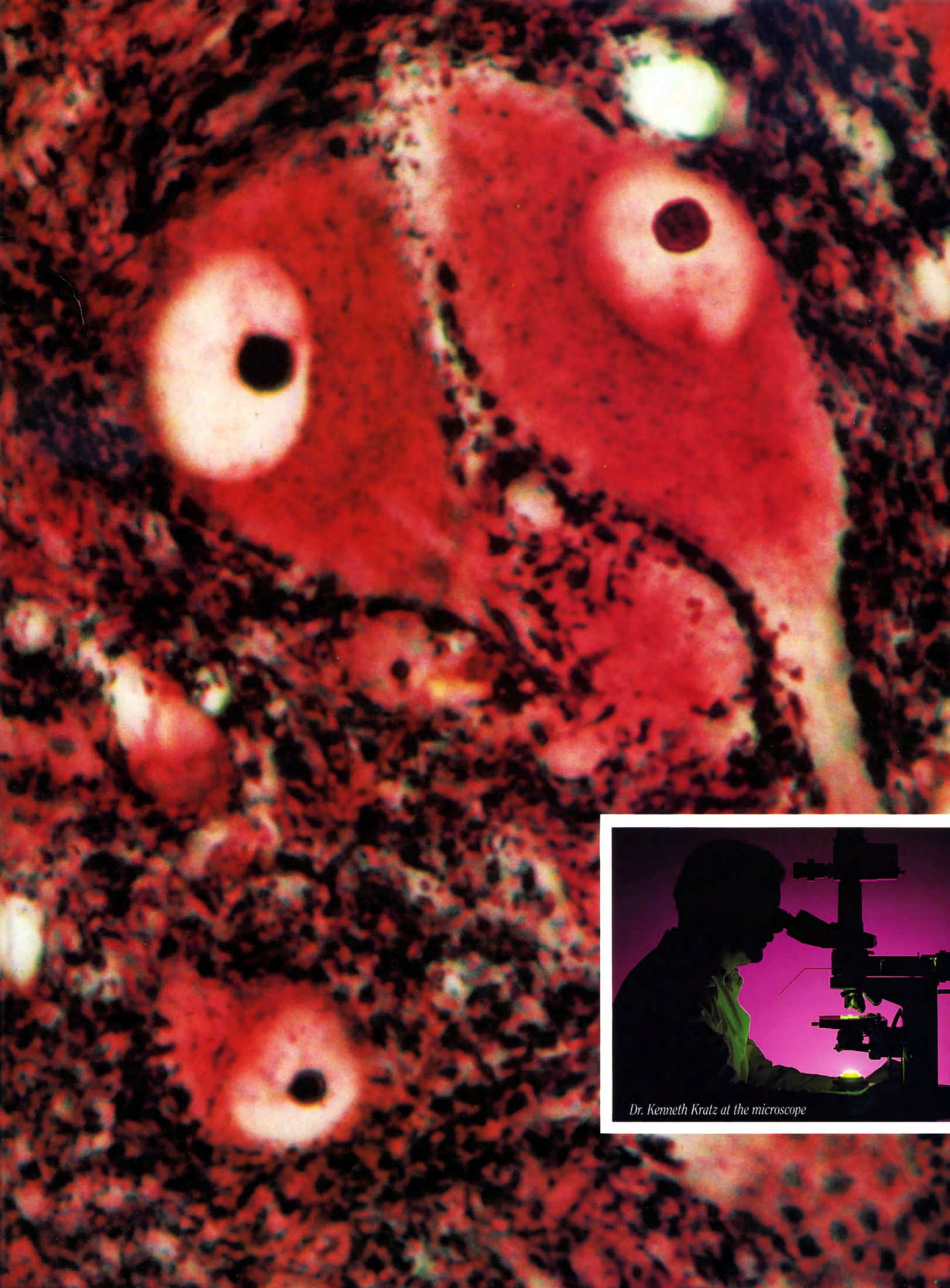


LSU NEUROSCIENCE

CENTER OF EXCELLENCE



Dr. Kenneth Kratz at the microscope

Neuroscience Center of Excellence

One of the most significant challenges to mankind is to understand the function of the brain—the center of thought, will, emotion and of the accumulation of knowledge. If, to this, is added the mystery of neurological and psychiatric diseases, most of which currently have no cure, the neurosciences truly deal with the frontiers of human knowledge—understanding how the brain works and how diseases evolve which affect it.

The Center bridges basic neurobiology with the clinical neurosciences by promoting collaborative research and actively fostering communication between the diverse disciplines. The interdisciplinary graduate training program in the neurobiology of disease, incentive grants awards, annual scientific retreats, and the ongoing neuroscience seminar program illustrate this integrated approach.

The LSU Neuroscience Center of Excellence gathers fundamental knowledge about the nervous system and the diseases which affect it. This emphasis on basic or "blue-sky" research is uncovering clues to identify events important for the survival, development and function of cells in the brain, retina, spinal cord and peripheral nerves. This wealth of new knowledge aims to contribute to the cure of nervous system diseases.

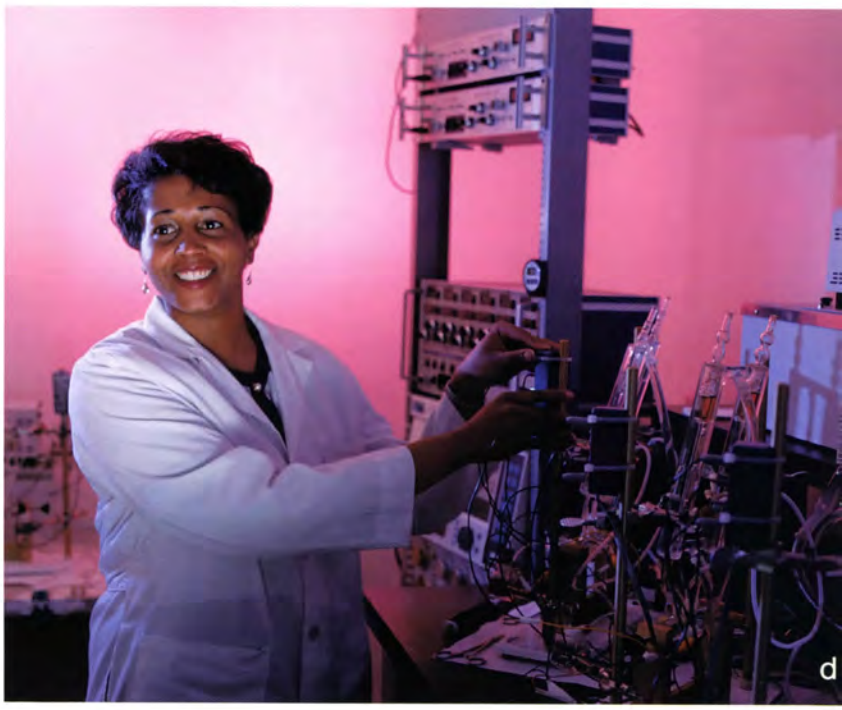
Since its inception in 1987, the scientific contributions coming from the Center have been impressive, and LSU is fast becoming recognized as a premier center for neuroscience research throughout the world. The Neuroscience Center has attracted over $20 million in research monies, including funds obtained from the Department of Defense to build 38,000 square feet of research space on top of the present Lions/LSU Eye Center building.

This influx of funding is creating a catalyst for real economic growth within New Orleans and the surrounding region. In a 1991 report, Dr. Timothy Ryan, Dean of the School of Business Administration at the University of New Orleans, estimated that the total economic impact of the Neuroscience Center in Louisiana could go as high as $99 million. From its success, the Center is developing new links to industry, enhanced relationships with biotechnology and pharmaceutical companies, and increased potential for attracting even more national research funding.

Each year, millions of people die or are disabled by neurological and psychiatric diseases. High quality, intensive research is our best hope for discovering why. The LSU Neuroscience Center of Excellence is at the forefront of this research, and its scientists are working diligently to bring new hope and understanding to the devastation of nervous system diseases.

Nicolas G. Bazan

Nicolas G. Bazan, M.D., Ph.D.
Director
LSU Neuroscience Center of Excellence



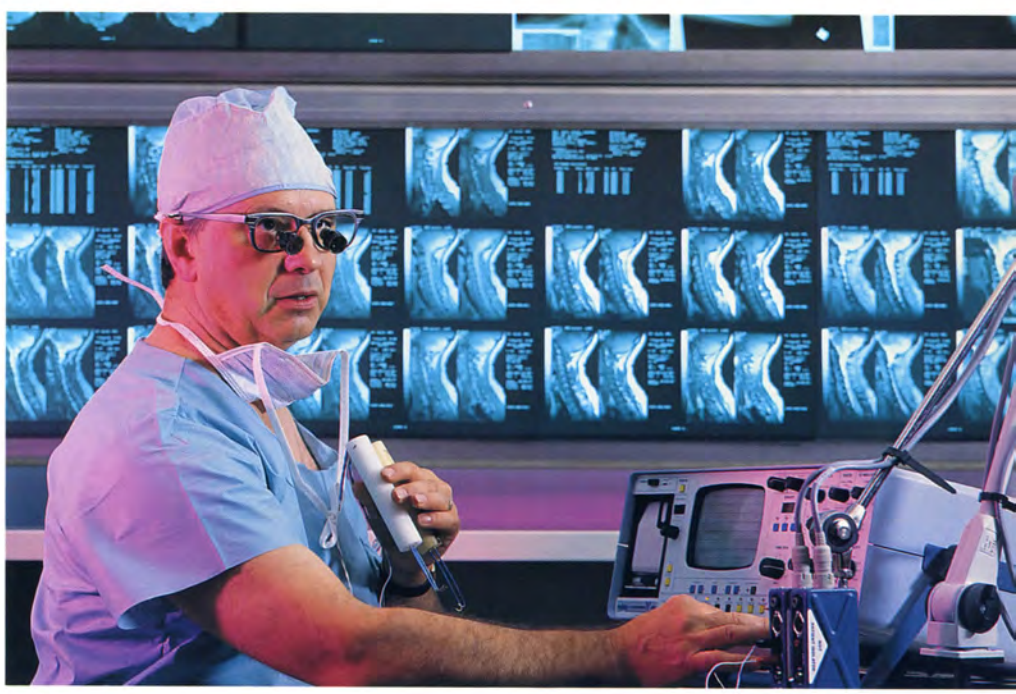
A. *Dr. Lee Happel uses electrophysiology to study peripheral nerve diseases.*

B. *Dr. Joseph Moerschbaecher, Professor and Head of Pharmacology and Experimental Therapeutics, studies a cross-section of a brain on an image analysis system.*

C. *Dr. R. Ranney Mize, Professor and Head of Anatomy, and Clinical Associate Grace Butler view brain tissue images generated by an electron microscope.*

D. *Dr. Rhoda Reddix, Assistant Professor of Pharmacology, conducts an experiment to investigate neuropathways that may be involved in gastrointestinal diseases.*

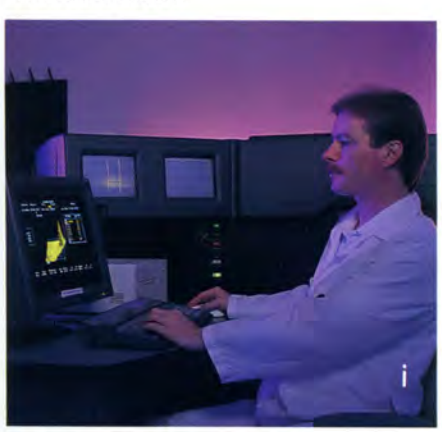
E. *Dr. David Kline uses special equipment to measure recovery of nerve function after surgery.*



F. *Dr. Diane Smith uses the electron microscope to study connections between nerve cells.*

G. *Dr. Austin Sumner teaches residents.*

H. *Neurologist Dr. Jay Rao analyzes human brain tissue from a patient who died with Parkinson's Disease.*



I. *Mr. Mark Griffin operates the cell-sorter from LSUMC core laboratories.*

Benefits to Louisiana and the Region

The LSU Neuroscience Center of Excellence has become a nucleus of academic excellence with tremendous benefits to Louisiana.

- A total economic impact estimated to be as high as $99 million *
- Attraction of research, development and related activites of pharmaceutical and biotechnology companies
- Increased federal research funding
- Creation of jobs
- Recruitment of outstanding professionals who have a significant economic, civic and cultural impact on the community
- Training of exceptional physicians, scientists and other health-related personnel
- Increased caliber of education
- Improved quality of life with the discovery of new treatments and rehabilitation for neurological and psychiatric diseases

* Source: ***The Economic Impact of the LSU Neuroscience Center of Excellence,*** Timothy P. Ryan, Ph.D., Dean College of Business Administration, University of New Orleans, October 1991.

Potential Links to Industry

- Over fifty pharmaceutical corporations and over forty start-up biotechnology companies have neuroscience goals compatible with the efforts of the LSU Neuroscience Center.
- Having emerged as an internationally recognized center for neuroscience research, pharmaceutical industry leaders are establishing ties with the LSU Neuroscience Center for purposes of doing collaborative research and developing new technologies to take into the marketplace.
- The LSU Neuroscience Center is combining its scientific strengths with the marketing efforts of the University of New Orleans Research & Technology Park to attract new medical businesses to New Orleans.
- The LSU Neuroscience Center is coordinating efforts with New Orleans' Downtown Development District to attract companies to the Biomedical Research Park which has been established to build on the strengths of New Orleans' medical industry as well as to promote urban renewal.

Programs in Progress

Educational

■ *Interdisciplinary Ph.D. in Neuroscience Graduate Program*

Offers interdisciplinary training leading to the Ph.D. in Neuroscience in which faculty from va departments at the LSU Medical Center and the University of New Orleans are involved

Attracts over 500 inquiries annually for four spots

Trains future teachers, researchers and clinicians for academic and industrial positions fulfilli for more exploration in the rapidly expanding neurosciences

Attracts highly qualified individuals to Louisiana seeking training

■ *Summer Undergraduate Neuroscience (SUN) Program*

Offers Louisiana's undergraduate students hands-on experiences in laboratory research and ed in the neurosciences

Anticipates a future need by encouraging students from a variety of cultural and educational b grounds to consider careers in the neurosciences and medicine

Encourages the best and brightest students to remain in or return to Louisiana to contribute mic excellence and to maintain the overall level of talent in their home state

In the near future, will incorporate high school students to share similar experiences and learn hand about careers in the neurosciences

■ *Neuroscience Seminar Series*

Offers in-depth, sophisticated discussion on interdisciplinary approaches to basic and clinical a of neurological diseases

Allows local neuroscientists to share their ongoing research

Enhances the educational climate in the neurosciences for faculty, fellows, residents and stude LSU Medical Center, the University of New Orleans, Tulane Medical Center, Xavier University a area academic institutions

■ *Distinguished Lecturer Series*

Attracts world renowned scientists, including numerous Nobel Laureates, to share their resear knowledge in the neurosciences

■ *Other*

Teaching to undergraduate medical, dental, allied health and nursing students throughout the LSU Medical Center

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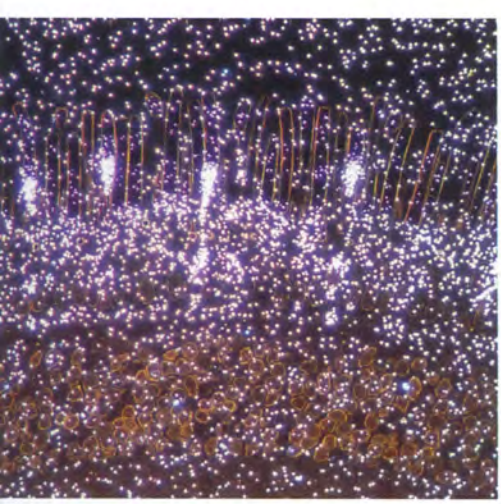
In the near future, will incorporate high school students to share similar experiences and learn firsthand about careers in the neurosciences



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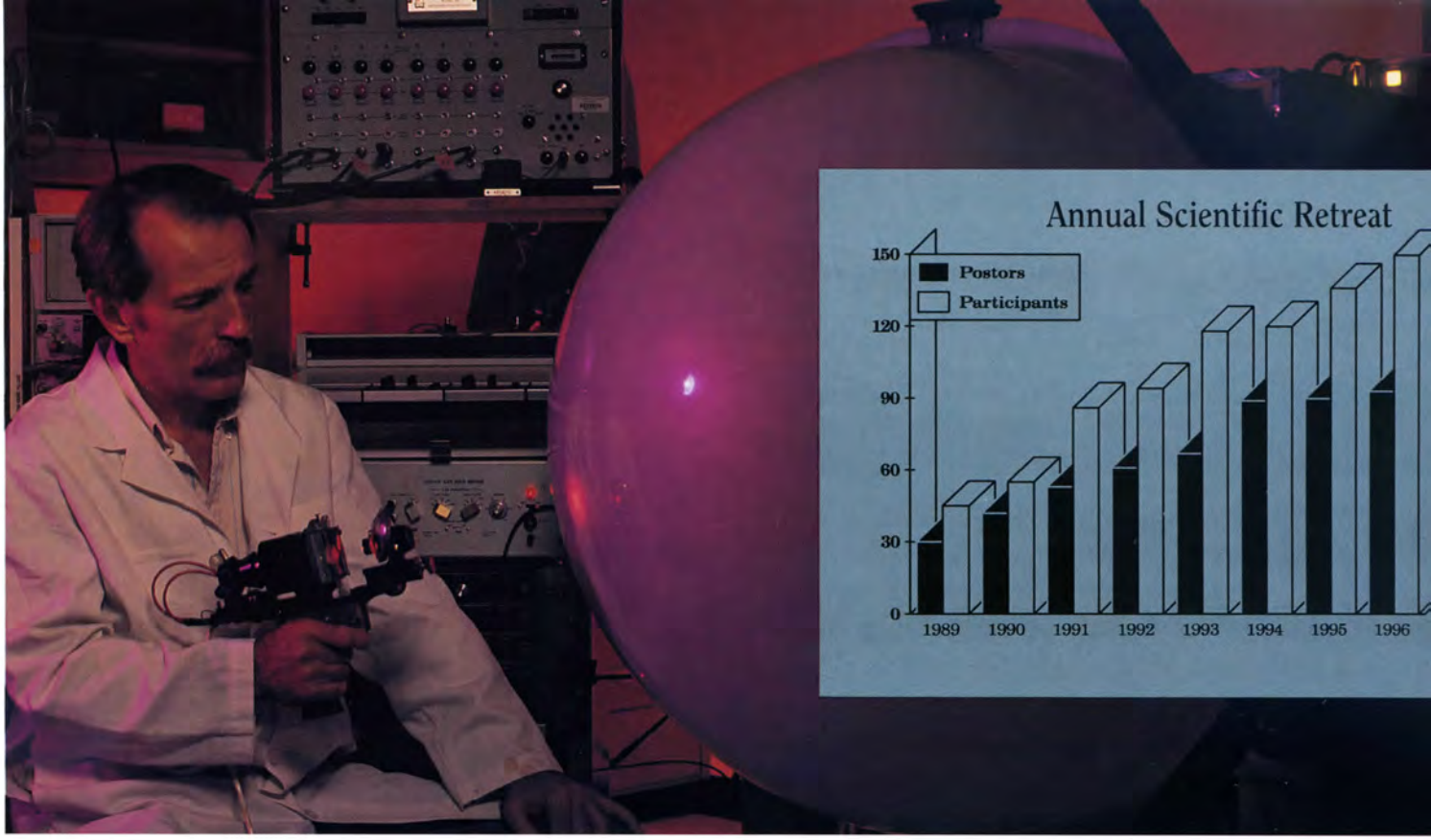


Research

- Ongoing Research

  Highly developed research programs in neurobiology and the clinical neurosciences with a focus on understanding stroke, blinding eye diseases, epilepsy, Parkinson's Disease, schizophrenia, alcohol and drug addiction, mental retardation, brain repair after injury, peripheral nerve function and other nervous system diseases

- Collaboration with the Army Medical Research and Development Command to study prevention, protection and repair of head injury

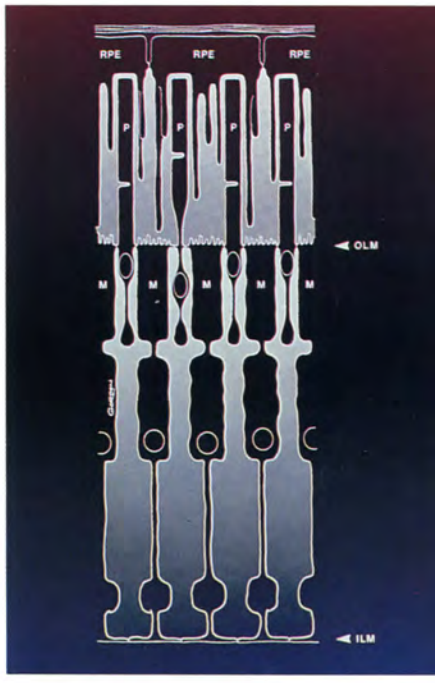
- Brain Tissue Bank for research (first of its kind in the South)

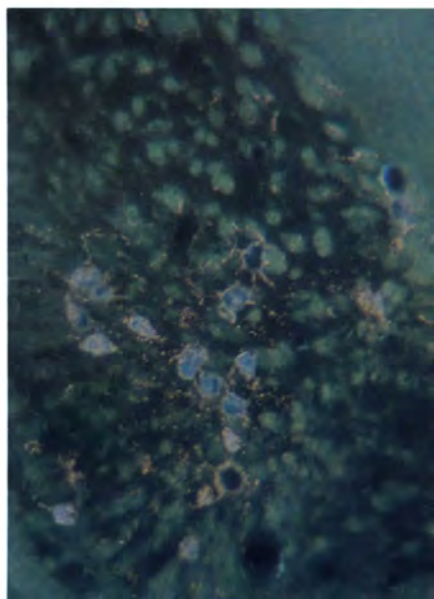
- Interdisciplinary Incentive Grant Program

  Open on a competitive basis to basic and clinical neuroscientists, this program stimulates new, promising interdisciplinary research in the neurosciences and leverages additional funding from out-of-state agencies

- Equipment purchases for enhanced research (image analysis systems, confocal microscopes, and calcium imagers, etc.)

- Collaborative research program in neurobiology and the clinical neurosciences with George Washington University





Growth and Development

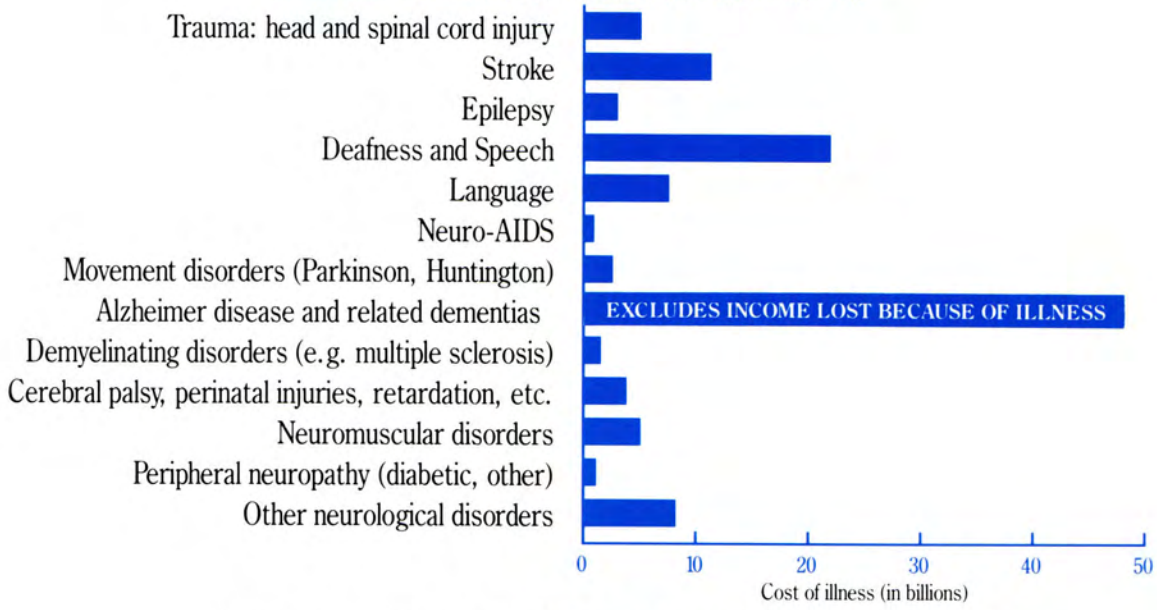
- Faculty recruitment to develop programs targeting specific diseases

- Annual Scientific Retreats and Workshops

- Development efforts to promote the Center, the potential of its investigators and its benefits to the community

ECONOMIC IMPACT OF THE MAJOR NEUROLOGICAL AND COMMUNICATIVE DISORDERS

(Source: National Institute of Neurological Disorders and Stroke, NIH)



These figures do not include the cost of blindness, estimated to be at least 22 billion dollars a year.

Programs to Develop

The goal of the LSU Neuroscience Center is to develop disease-specific programs which bridge the basic and clinical sciences with the diagnostic and therapeutic processes. This goal will serve the purpose of expediting the transfer of knowledge from the bench to the bedside, bringing new prevention and treatment modalities to the patient sooner. Below are the primary focus areas ready for development.

Stroke and cerebrovascular disease

Alzheimer's Disease and age-related dementias

Learning Disabilities (Dyslexia): developmental neurosciences

Mental Depression: biological and molecular basis

Alcohol and Drug Addiction: molecular neuropharmacology

Neurodegenerative Diseases such as Amyotrophic Lateral Sclerosis and Parkinson's Disease

Brain Repair After Injury: growth factors

Molecular Biology of Neurological Diseases with a focus on mental retardation and those caused by perinatal events

Nicolas Bazan M.D. Ph.D. and Sir John Vane

The Importance of "Blue-Sky" Research

—Excerpts from a talk by Sir John Vane, March 13, 1995, New Orleans, LA

Academic, or basic, or "blue-sky" research, holds great promise for the community and for the health of mankind. But today's urgency to show a return on investment is leading pharmaceutical companies to demand that research be project and market oriented, so much so that "blue-sky" research is threatened. This industry threat is very real and is spreading to governmental funding of academia because of the same short-sighted philosophy.

I will give some examples from my own experience which illustrate the way in which "blue-sky" research can lead to totally unexpected benefits for the health of mankind. The first is aspirin.

Just under 100 years ago in the German drug company Bayer, a chemist called Felix Hoffmann was asked by his father, who was taking salicylate for his rheumatism, whether anything could be done to improve its bitter taste. Felix Hoffmann then invented aspirin by adding a simple side-arm to the salicylate molecule. This was the beginning of Bayer aspirin and nowadays hundreds of thousands of tons of aspirin are used around the world for the treatment of headaches, rheumatism, fevers and so on. But nobody knew how it worked until some 25 years ago.

My laboratory was working on a group of chemical messengers formed in many parts of the body called prostaglandins. At the time, it was becoming clear that certain prostaglandins were involved in causing inflammation and fever. I was writing a review over the weekend at home when suddenly it occurred to me that maybe aspirin and similar drugs were working by preventing the body from making these prostaglandins. In the laboratory on Monday morning I said to my colleagues, "I think I know how aspirin works!" I am not a biochemist and so I had never made enzyme preparations before. I went to the literature and found out something about the enzyme which make prostaglandins in the body. I prepared it in a test-tube and then added different doses of aspirin and other similar substances, including morphine, as control. I found that aspirin, or an aspirin-like drug, reduced the production of prostaglandins by this enzyme according to dose.

An especially fertile area for basic or "blue-sky" research is of course the brain. This has been left to last by scientists because of the enormous technical difficulties of studying the brain.

After repeating the experiment in many different ways in different tissues, I published the results in the prestigious journal Nature in 1971 and suggested that the mechanism of action of aspirin and similar compounds was through the prevention of the formation of these substances known as prostaglandins. The idea was that prostaglandins were released in pathological excess in inflammation and if these could be removed, then you would suppress the fever, pain and swelling of inflammation. At the same time, we knew that all aspirin-like drugs tended to irritate the stomach and may lead to kidney problems, and so I suggested that these side-effects were due to the removal of prostaglandins that were essential for the proper functioning of the stomach and the kidneys.

The theory was generally accepted and has stood the test of time. More importantly, it was the discovery of the basic mechanism of action that has led to the use of aspirin in cardiovascular disease.

We have known for some time that heart attacks and strokes are caused by the inappropriate clumping together of platelets within the circulation. Platelets are the smallest particles in the bloodstream and their only function is to stop us from bleeding to death. Normally, when we cut ourselves, armies of platelets clump together and stick to the walls of the cut, building up a dam to stem the flow of blood. The same sort of process may happen inappropriately in a coronary artery or in an artery going to the brain and cause a blockage, leading to a heart attack or stroke. After our discovery of how aspirin works, it became clear that platelet clumping was due to the formation of a prostaglandin-like substance in the platelets. Thus, knowing the mechanism of action, people started to test whether aspirin may prevent the inappropriate clumping of platelets which leads to heart attack and strokes.

First of all they started out with large doses, the sort of dose (6 tablets a day) that was used in rheumatoid arthritis. However, over the years, clinical trials in thousands and thousands of people have shown that only a small dose is needed and that even a baby aspirin (75 mg or ¼ of a normal tablet) taken once a day is sufficient to prevent the platelets from sticking together. This is such a small dose that in lectures I jokingly say that we should keep an aspirin tablet in the bathroom cupboard and lick it every morning! Indeed, clinical trials worldwide have shown that taking an aspirin every day reduces the risks of a heart-attack or a stroke by up to 50%. So there are many thousands or even millions of people who are alive

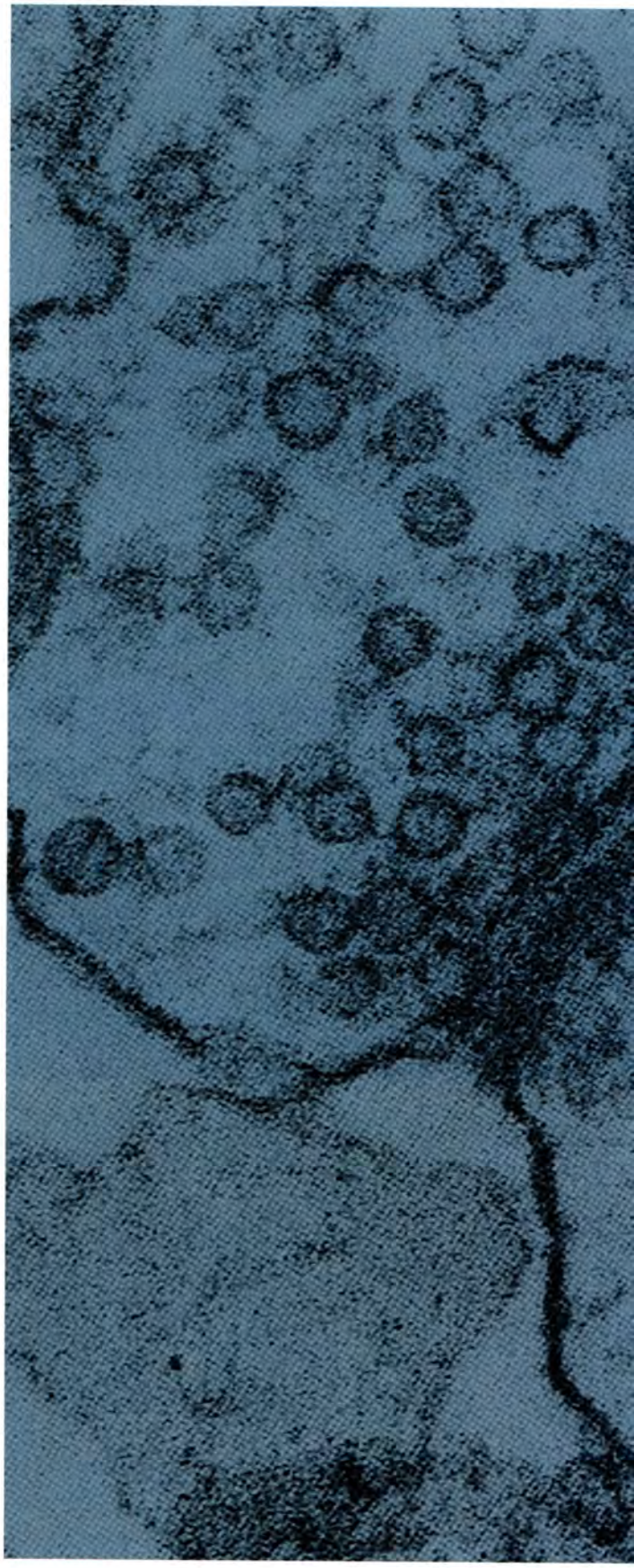
today because they take a daily aspirin for the prevention of heart-attacks and strokes who would not otherwise have been with us had I not done that crucial experiment on a Monday morning. That is directly a result of our "blue-sky" research.

My second example comes from the same family of prostaglandins. Anatomists over the generations have known that blood stays fluid in healthy arteries but clots in dead ones. This was never understood but we also knew that the very same platelets that I have been talking about do not normally stick to the inner healthy walls of arteries. In 1976, we found that this was because the inner walls of the arteries make a prostaglandin which prevents the platelets from sticking to them. We called it prostacyclin and this work opened up an enormous field of research. We now think that platelets stick to arteries when compounds such as prostacyclin fail to be formed. However, the therapeutic importance of this finding is that prostacyclin-like substances are now being marketed for use in obstructive vascular diseases such as those that normally lead to foot or leg amputations.

My third example shows how a new important kind of drug can come through serendipity, international collaboration and of course, blue-sky research.

In the mid-1960s when I was working at the Royal College of Surgeons in England, I had an application for a post-doc position from a Brazilian scientist named Sergio Ferreira. For his Ph.D., he had worked on the venom of a particularly nasty Brazilian snake called Bothrops Jararaca. He had shown that extracts of this venom contained small peptides which potentiated the action of a pain-producing substance in the venom called bradykinin, probably by enzyme inhibition.

He came to my laboratory carrying some of his venom extracts in his pocket. I suggested to Sergio that we should study his snake venom extract on the renin angiotensin system, so called because an enzyme called renin is released from the kidney into the bloodstream and leads to the formation of a very strong pressor substance called angiotensin. However, he had other plans. He wanted to continue his work on bradykinin and being a forceful personality, he convinced me to let him do that. We worked together on bradykinin for two years and only at the end of that period did I persuade another colleague, Mick Bakhle, to test the snake venom on the renin-angiotensin system. It turned out to be a potent inhibitor of a key enzyme (angiotensin converting enzyme or ACE) in that system.



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