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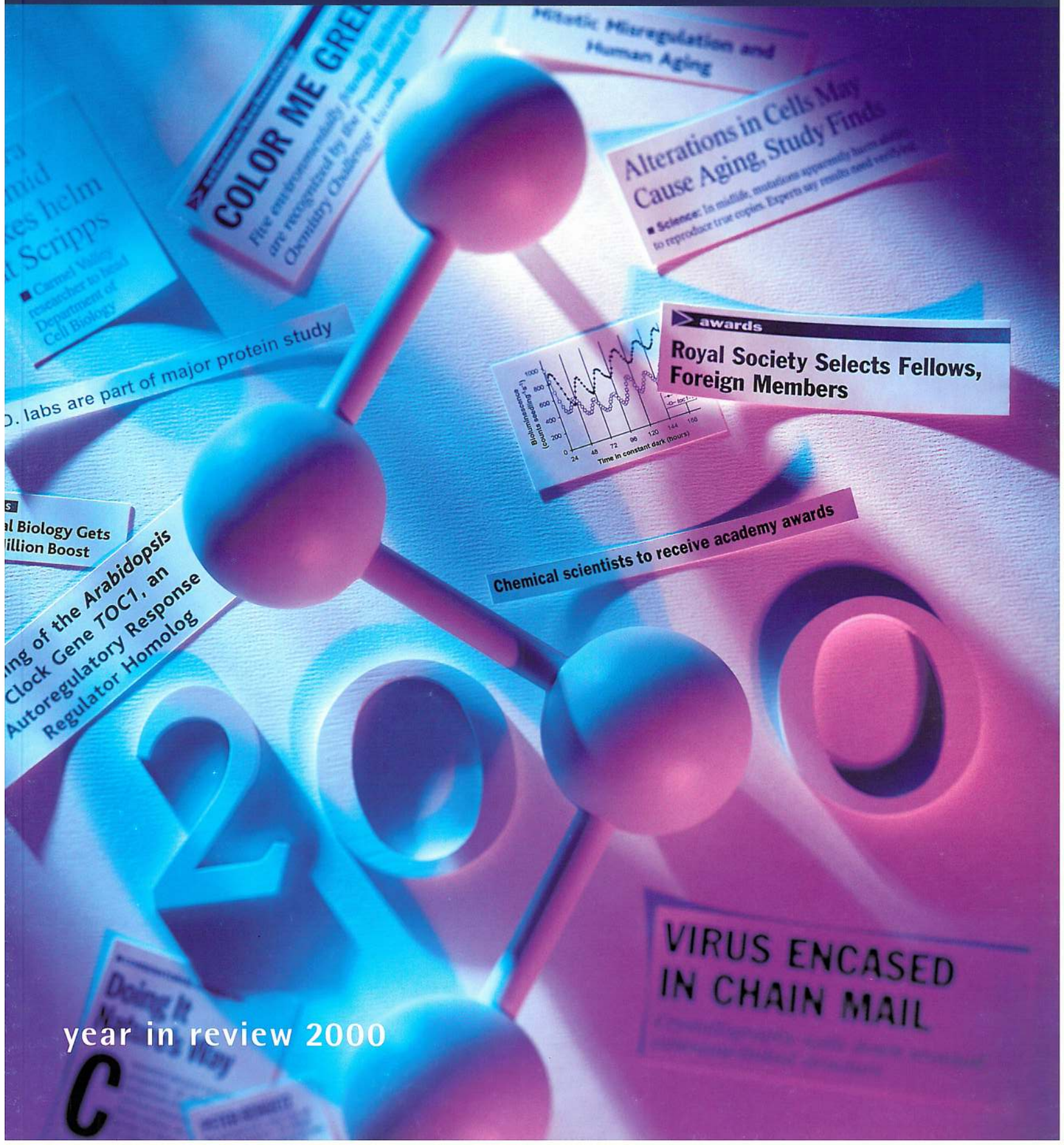
THE SCRIPPS RESEARCH INSTITUTE

Endeavor



year in review 2000

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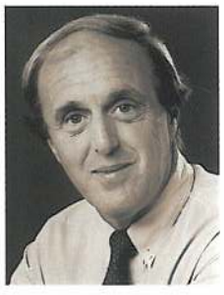


This has been a year of significant transition at The Scripps Research Institute, all the while maintaining its impressive array of scientific accomplishments, facilities expansion to accommodate ongoing growth, and important new faculty appointments. Sadly, this year marked the passing of TSRI's Dean of Graduate Studies and Chairman of the Department of Cell Biology, Norton B. Gilula, Ph.D., after a valiant struggle with cancer. While he has made an indelible imprint on the quality and character of the Institute, we all miss his keen insights, sound scientific judgement, generosity of spirit, leadership ability, and friendship. It is a great loss to the scientific community here.

Jeffery Kelly, Ph.D., Lita Annenberg Professor, Department of Chemistry, and The Skaggs Institute for Chemical Biology, has been appointed Acting Dean, Graduate Studies Program, and Acting Vice President, Academic Affairs, taking over many of Dr. Gilula's responsibilities. While conducting an active program of laboratory studies, Jeff will assist me with policy decisions that relate to the direction of scientific activities at the Institute. In addition, Sandra L. Schmid, Ph.D., has replaced Dr. Gilula as Chairman, Department of Cell Biology. She has been a member of TSRI's faculty for more than 10 years where she has distinguished herself as an outstanding scientist whose work is widely respected in the international scientific community.

TSRI continues to enjoy a collegial and productive relationship with Novartis, which recently granted a five-year renewal on its industrial collaboration agreement with the Institute. Clearly, this arrangement is of paramount importance to the continuation of TSRI's long-range initiatives and we expect many more years of fruitful efforts.

With more than 1,000 manuscripts submitted for publication by TSRI's scientists, it is difficult to single out a small number of scientific accomplishments from this substantial group of discoveries. However, an iteration of a few will connote the breadth of achievements in a multiplicity of research arenas.

Carlos Barbas, Ph.D., Professor, Department of Molecular Biology, and a member of The Skaggs Institute, has developed a method of producing and combining proteins as modular building blocks capable of functioning as genetic switches to turn on or off genes on demand. Barbas calls this "an operating system for genomes." Its goal is to develop a new class of therapeutic proteins that can inhibit or enhance the synthesis of proteins, providing a new strategy for fighting diseases of either somatic or viral origin. The lab is currently developing proteins that may inhibit the growth of tumors, halt HIV, and even make healthier corn. They have demonstrated that they can use their alphabet of proteins to specifically turn on or off genes at will.

A team of scientists studying a human DNA repair enzyme, led by John Tainer, Ph.D., Professor, Department of Molecular Biology and The Skaggs Institute, has discovered an evolutionary adaptation that highlights a fundamental advantage in the way human cells repair damage to their DNA. They have demonstrated that a key DNA repair enzyme is optimized to remain bound to its toxic, damaged DNA products until the next enzyme in the DNA repair pathway can take over. This adaptation allows for DNA repair in human cells to be coordinated between subsequent enzymes in the pathway, rather than having harmful DNA damage intermediates exposed in the cell. This has implications, for example, in cancer chemotherapy regimes because it may be possible to overwhelm DNA repair processes when the amount of damage is very high.

Work in my laboratory this year, in collaboration with Peter Schultz, Ph.D., Professor, Department of Chemistry and The Skaggs Institute, and Director, Genomics Institute for the Novartis Research Foundation, has shown that gradual genetic changes may be the source of many, if not all illnesses of aging, including breast cancer, osteoporosis, Alzheimer's disease and arthritis. The study concludes that human aging and its associated diseases can be traced to a gradual increase in cell division errors in tissues throughout the body. This functional change begins slowly in middle age and increases gradually with advancing age. While scientists had previously believed that aging is a disease in which cells stop dividing, this study suggests that aging is a disease of quality control. With advancing age, altered gene expression results in cells with diminished function. Errors in cell division lead to the altered expression of a collection of key genes in the cells. Altered gene expression gradually causes the loss of tissue function which results in aging.

Researchers led by Chi-Huey Wong, Ph.D., Professor, Department of Chemistry and The Skaggs Institute for Chemical Biology, have a new tool to address the growing problem of antibiotic resistance. They have focused on aminoglycosides, a family of antibiotics that includes such drugs as neomycin. Bacteria, which create the proteins they need to survive, are constantly evolving and mutating in ways that circumvent the activity of antibiotics. To circumvent the problem, Wong has found a way to bind the antibiotic to the bacteria's RNA. This prevents the formation of proteins that allow the bacteria to become resistant to antibiotics. The approach could yield a drug 1,000 times more effective than the original antibiotic.

The buildout of the facility to house the new Institute for Childhood and Neglected Diseases continued this year with the first scientists expected to take occupancy of their laboratories in January, 2001. When fully occupied, this facility will house some 150 scientists and support staff. John and Rebecca Moores' unique contribution of a collection of rare automobiles and a collection of important U.S. coins was auctioned on TSRI's behalf, the proceeds of which have provided the lead gift toward the establishment of the institute.

Scientists and clinicians selected to participate in The Skaggs Clinical Scholars Program, established with a contribution of $2 million from the Skaggs Family, have completed their first year of collaboration. Chaired by Ernest Beutler, M.D., Chairman, Department of Molecular and Experimental Medicine, the goal of the program is to more closely integrate clinical and basic research within the Scripps organization by selecting research-oriented clinicians and funding meritorious collaborative research projects between each clinical scholar and a TSRI scientist. The broader goal is to

expand the body of knowledge related to human disease and to develop effective therapeutic interventions.

A number of prominent researchers joined the scientific staff at TSRI this year, bringing the number of faculty members to more than 275. They include Joel N. Buxbaum, M.D., former Professor of Medicine, NYU School of Medicine; Bruce Beutler, M.D., former Professor, University of Texas Southwestern Medical Center at Dallas; Dong-Er Zhang, Ph.D., former Assistant Professor, Department of Medicine, Harvard Medical School; Heidi Stuhlmann, Ph.D., former Assistant Professor, Brookdale Center for Developmental and Molecular Biology, Mount Sinai School of Medicine; John R. Yates, Ph.D., former Associate Professor, Molecular Biotechnology, University of Washington; Mark R. Mayford, Ph.D., former Assistant Professor, Department of Neurosciences, University of California, San Diego; Aniko Bartfai, Ph.D., former Associate Professor, Department of Psychology, Stockholm University; Ulo Langel, Ph.D., former Associate Professor, Department of Neurochemistry and Neurotoxicology, Stockholm University; and Geoffrey Chang, Ph.D., who recently completed a postdoctoral fellowship at CalTech.

This year, as in years past, numerous TSRI faculty have been recognized by their peers with prestigious awards and honors. K. Barry Sharpless, Ph.D., Professor, Department of Chemistry and The Skaggs Institute, has been selected to receive the National Academy of Sciences Award in Chemical Sciences. The prize is awarded for innovative research that contributes to a better understanding of the natural sciences and to the benefit of humanity. Ian Wilson, D.Phil., Professor, Department of Molecular Biology and The Skaggs Institute, has been elected to fellowship in the Royal Society, the independent scientific academy of the UK founded in 1660, dedicated to promoting excellence in science. Chi-Huey Wong, Ph.D., Professor, Department of Chemistry and The Skaggs Institute, has been selected to receive a 2000 Presidential Green Chemistry Challenge Award, jointly presented by the Director of the U.S. Environmental Protection Agency, the Director of the White House Office of Science and Technology and the President of the American Chemical Society. The award program provides national public recognition for organizations that are successfully researching, developing and implementing outstanding green chemical technologies.

As we enter a new millennium, I feel that TSRI is in a unique position to exploit the riches of the sequencing of the human genome, to expand on the prodigious body of knowledge elucidated by our own faculty, to play a role in training the next generation of scientists through the Graduate Studies Program, and to ultimately have a positive effect on alleviating human suffering.

Richard A. Lerner, M.D.

Sandra L. Schmid, Ph.D.
Chairman
Department of Cell Biology

K.C. Nicolaou, Ph.D.
Chairman
Department of Chemistry

Cell Biology

Sandra L. Schmid, Ph.D., Chairman

While human genome sequencing has provided a list of all cell components, their functions are still largely unknown. Answering these questions will drive research in cell biology well into the new millennium. The recently acquired genetic blueprint provides a foundation for the new discipline of functional genomics, a mining expedition that goes into the depths of cell biology to link an individual's genetic organization with their physiology. The Department of Cell Biology is uniquely positioned to exploit the vast information base of the human genome. Using sophisticated tools, its scientists are placing newly identified genes within their functional context. Understanding the operation of the living cell will help create new therapeutic approaches to treating cancer, heart, lung, muscle, and retinal and neurodegenerative disease.

Drs. Velia Fowler, Bill Balch, Sandy Schmid and Larry Gerace are teasing apart the complex biological processes that govern cell motility, the biosynthesis of essential cellular proteins, the uptake of essential nutrients and hormones, and communication between the nucleus (where the genome is stored and where gene expression is initiated) and the cytoplasm (where the protein products of the genome are synthesized). Fowler's work on muscle cell development provides insight into cardiac disease and muscular dystrophy. Cystic fibrosis is a disease caused by the aberrant synthesis and intracellular transport of a protein essential for maintaining fluid balance in the lungs. By identifying and characterizing the cellular machinery and processing pathways, Balch's work is aimed at providing more effective avenues for its treatment. Schmid has discovered that a protein associated with membrane dynamics at the cell surface may function as a cellular gatekeeper, ready to respond to invasion or disruption of the cell's membrane barrier. This protein may provide a new target for eradicating cancer cells.

Accessing the huge amounts of information in the genome is aided by knowing the functional context in which each gene product is expressed. John Yates, Ph.D., a recent recruit to the department, is a pioneer in this new area of research called proteomics. His laboratory has developed sophisticated tools and computer programs that enable the detection of protein differences between normal cells and cancer cells, allowing identification of a potential weakness that can be targeted by therapy. Categorizing proteins in functional sets is a valuable approach to mining the human genome.

To view the dynamics of living cells and the machinery within, Klaus Hahn, Ph.D., has developed innovative chemical biosensors that can be attached to proteins. When the protein is switched on or after a specific biochemical reaction, the biosensors emit a fluorescent light that can be easily followed with a microscope and a digital movie camera. In a related effort, Clare Waterman-Storer, Ph.D., has created fluorescent-tagged molecules that emit light as they assemble themselves into larger cellular machines. With these new methodologies, researchers can now watch cells respond to intercellular signaling in real time, and follow these events within living cells — the same environment in which all genes and proteins interact. These techniques could provide the basis for high through-put screens to identify drugs that block metastasis of cancer cells, or the infiltration of blood cells leading to cardiac disease.

TAKING ADVANTAGE OF THE GROWING KNOWLEDGE OF THE GENOME

A comprehensive understanding of how proteins function requires knowledge of their structure. Crystallography and NMR structural analysis yield structural information on individual proteins or small protein complexes, but cellular machines are often composed of multiple proteins inaccessible to conventional structural analysis. The department has assembled a world-renowned center employing electron microscopy to create high-resolution structural images of large molecular complexes. Using these techniques, Ron Milligan, Ph.D., has examined the tiny motors that cause muscles to contract, and has unveiled the elegant means by which they generate force and movement. Mark Yeager, M.D., Ph.D., has solved the structures of viruses revealing their susceptibility to intervention, and the structure of cardiac GAP junctions that coordinate heart beats.

In the human body, specialized cells work together to govern physiology. Steve Kay, Ph.D., studies the

effect of biological clocks and the proteins that make them run. Recently, he discovered that these clocks operate on the cellular level. Clock components actually perceive light, so that daily activities are coordinated with sunrise and sunset. Ben Cravatt, Ph.D., has identified a new class of signaling molecules generated in the brain that control sleep and other brain activities. Others in the department, including Shelley Halpain, Ph.D., and new recruits, Drs. Ardem Patapoutian and Mark Mayford, are dissecting the nervous system to discover how we learn and how our sense of touch develops.

The breadth and depth of the department is a tribute to the pioneering leadership of its late Chairman, Norton B. Gilula, Ph.D. Using and developing new investigative tools that range from proteomics, to the biochemistry and structure of complex cellular machines, to high resolution images that let researchers observe in-cell dynamics in real time, cell biologists are poised to take advantage of our growing knowledge of the genome. In the coming years they will better understand the machinery and mechanisms governing the complex cellular processes essential for life and their role in health and disease. ■

Chemistry

K.C. Nicolaou, Ph.D., Chairman

Researchers in the Department of Chemistry conduct scientific inquiries at the frontiers of chemical synthesis, combinatorial chemistry and chemical biology. These disciplines are crucial to understanding human biology and comprise critical new components of modern drug discovery and development. The approximately fifteen faculty members in the department are distinguished teacher-scholars engaged in a broad spectrum of independent research programs in areas as diverse as biological and chemical catalysis, natural products synthesis, molecular design, chemical evolution, materials science, and chemical biology.

Working at the interface of chemistry and biology, faculty members continue to collaborate extensively with biologists and clinicians to uncover the mysteries of a range of biological processes and combat human disease. Through these interdisciplinary research programs, the power of chemistry is brought to bear on numerous biological problems that may one day lead to biomedical breakthroughs and create new, and much needed, medicines and therapeutics.

Faculty members target architecturally novel and biologically-active natural products for total synthesis to discover and invent new synthetic technologies that may help facilitate further biomedical research, and for their relevance to future medical treatments. In their search for these molecules, researchers are often challenged to develop novel synthetic strategies and create new synthetic technologies. At the same time, they take advantage of the opportunity to design and synthesize analogs of naturally occurring substances in the hope that they might have superior pharmacological profiles. As a result of these related efforts, scientists in the department have synthesized a number of such natural and designed molecules and discovered several with promising pharmacological profiles. Currently, several new projects are directed toward the chemical synthesis of antitumor, antibiotic and antiviral agents, and other molecules with health-modulating properties.

A number of faculty members and their research groups are engaged in combinatorial chemistry, a process that has revolutionized the drug discovery process, and promises to have a major impact on biology and medicine in the future. Combinatorial chemistry involves the synthetic assembly of novel molecules in various combinations to produce large libraries of thousands — often millions — of compounds for drug screening purposes or specific chemical properties. The screening of these libraries of compounds against specific biological targets often leads to the discovery of new tools or compounds that can, once their molecular structures are refined, become leading drug candidates. From such programs, several enabling technologies for biology and medicine have been developed, and a number of promising compounds that regulate important biochemical pathways have been discovered.

The basic principles of combinatorial chemistry have their origins in nature, where random mutations often lead to vast numbers of biomolecules that undergo subsequent selection and evolution. Mimicking such practices, a number of laboratory groups in the department have devised new protocols for the generation and selection of useful biomolecules such as catalytic antibodies

and nucleic acids that facilitate important chemical reactions. Together with other catalytic systems developed in the department—both naturally occurring and synthetic—these catalysts are being used to accelerate certain chemical processes and facilitate new biomedical applications.

Cutting-edge molecular recognition studies are part of the department's ongoing activity that may help provide fundamental insights into the ligand-biomolecule interactions. Such endeavors, aside from their unique artistic appeal, are helping delineate basic molecular architectures and require precise molecular design and sophisticated chemical synthesis techniques. As a result, they often lead to a far greater understanding of molecular assembly processes that may facilitate the design of potential drug candidates. Department researchers are developing designs for enzyme inhibitors, important agents that can block the underlying mechanisms of certain diseases. Several promising compounds of this type have been identified through chemical and enzymatic synthesis followed by biological screening.

In addition to the diverse studies on the large biomolecules such as proteins, DNA, RNA, and polysaccharides, a number of laboratories are focused on research aimed at understanding small segments of these superstructures, namely peptides, oligonucleotides, and oligosaccharides and small organic ligands. The potential benefit of this work includes new antibiotics, antiviral agents, and treatments for diseases such as Alzheimer's, cancer and AIDS. Chemistry relating to the possible origins of life on earth using such designed molecules is also being explored.

With the sequencing of the human genome nearly complete, chemistry is poised to make decisive contributions in the search for new medicines to treat modern disease. While the discipline will be crucial in the development of the evolving field of proteomics (the identification and understanding of the function of the body's protein network), chemists face the challenge of designing and synthesizing the millions of molecules needed to select those ligands that can regulate disease-relevant biological targets with far better outcomes. With its talented and motivated faculty and students, the Department of Chemistry is well positioned to capitalize on the new genetic information available, and exploit the enormous opportunities that lie ahead. ■

Immunology

Richard J. Ulevitch, Ph.D., Chairman

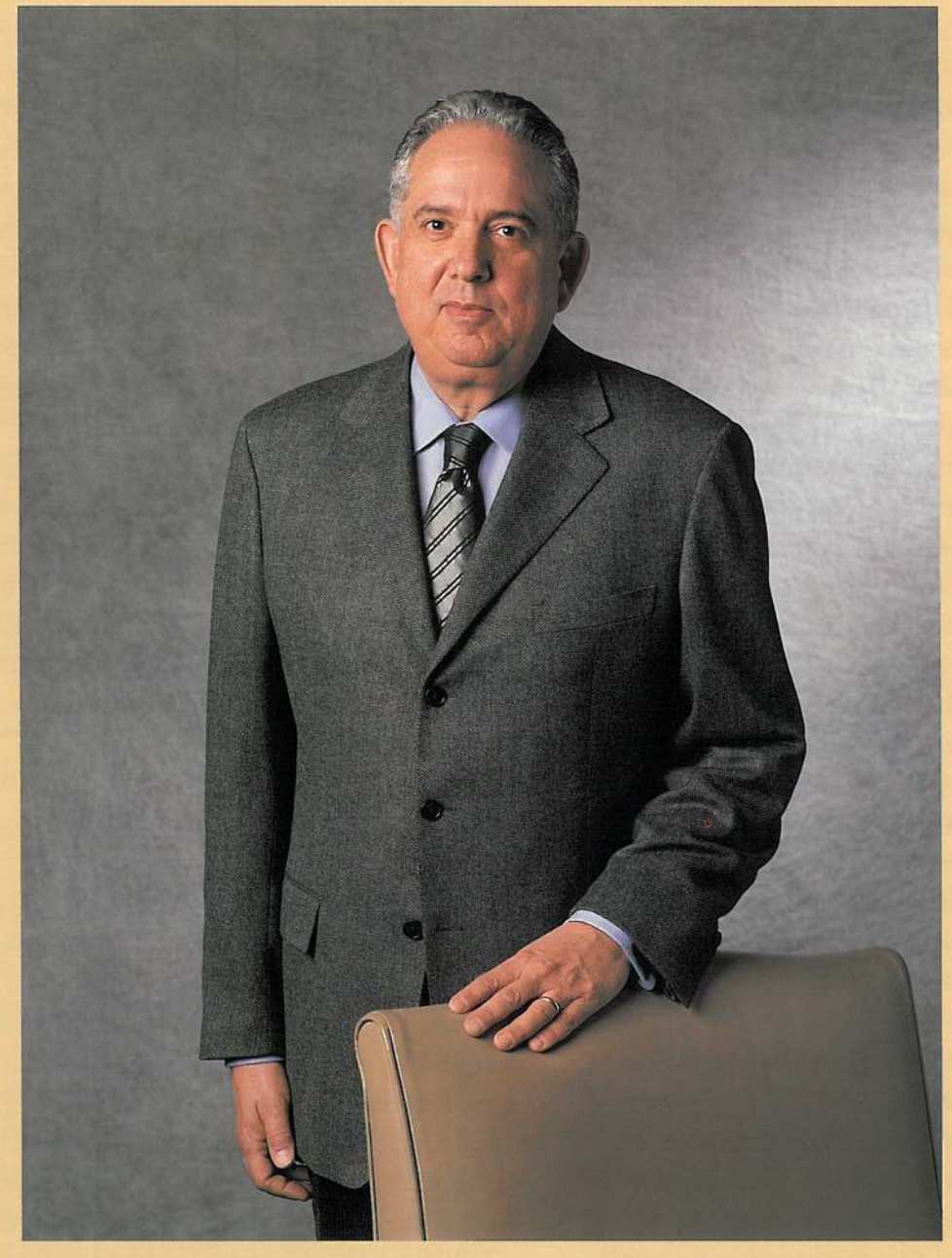
Today, more than ever, the ability to manipulate the immune system assumes increasing importance to improved medical care throughout the world. Scientists in the Department of Immunology feel a responsibility to focus their research efforts on understanding the immune system in ways that will allow for practical and effective solutions to worldwide health problems, including cancer and infectious disease. Important research advances are making the possibility of immunotherapy a reality for many types of tumors. New therapies include active cell-based immunotherapies based on novel methods to stimulate dendritic cells ex vivo.

Infectious disease is another area in which immunology may provide solutions to newly emerging medical problems. News reports are prevalent about E.coli-tainted food and water supplies, the devastating effects of HIV on the African continent, and the appearance of West Nile virus in urban centers in the United States. Solutions will depend on scientists' ability to effectively use the immune system to combat or prevent these types of infections.

FUNDAMENTAL UNDERSTANDING OF THE INNATE IMMUNE SYSTEM

Researchers in the department are addressing these challenges in many important ways. They continue to receive international recognition for their inquiries into the fundamental mechanisms of immune responses to pathogens. In recent years the department has built expertise in areas that directly impact our understanding of nearly all aspects of the innate immune system. Of particular importance this year was the recruitment of Bruce Beutler, M.D., Ph.D., who moved his research team to TSRI from The University of Texas Southwestern Medical Center at Dallas. Beutler is credited with several major discoveries that have changed scientists' understanding of how the innate immune system recognizes and responds to pathogens.

The department's research teams have contributed many seminal findings that shape current concepts of operation of the innate immune system. Among the past accomplishments is the recognition of the importance of



Richard J. Ulevitch, Ph.D.
Chairman
Department of Immunology

LPS binding protein and CD14 in pathogen recognition. These fundamental discoveries have provided the basis for a phase II clinical trial to test anti-CD14 monoclonal antibodies in septic shock.

The department is well recognized for the efforts of its faculty to better understand the basic biology of HIV infection and the immune response to HIV. A number of advances have been made that promise to have a positive impact in this area of research. In particular, studies using targeted dendritic cell immunization point to new opportunities in vaccine design for both infection and cancer.

A better understanding of how lymphocytes regulate antibody production is also essential for designing better approaches to manage infection. During the past year, the department has expanded its knowledge about crucial mechanisms involved in B cell development. This includes understanding the principles of receptor editing and peripheral immune tolerance.

In viral infection the T lymphocyte plays an essential role in eliminating infected cells and limiting the spread of virus. Understanding how T cell populations are selected in the thymus and proliferate in the periphery is a central and as yet unsolved issue. A number of scientists, working collaboratively with their colleagues in the Department of Molecular Biology, continue to uncover new structural information about essential receptor proteins of the immune system, adding to the body of knowledge of how T cells work at the most fundamental levels.

There are a number of very successful programs within the department performed in close collaboration with Novartis Pharmaceuticals. This is particularly important because of the immense potential for translating knowledge of the immune system into practical measures to control or eliminate serious human disease.

In addition, many professors in the department are active participants in the Graduate Studies Program. In the summer, the labs are filled with the presence of high school and college students working in internship programs. In addition to an active weekly seminar program under the auspices of the Immunology Affinity Group, the department continues to organize an annual symposium now in its 7th year. This program brings together internationally recognized scientists working directly or indirectly in areas important to immunology. ■

Molecular Biology

Peter E. Wright, Ph.D., Chairman

Scientists in the Department of Molecular Biology use the twin tools of molecular genetics and structural biology to investigate a wide variety of important biological processes. Research continues to make progress toward a better understanding of the fundamental processes of living organisms such as the molecular actions in cell cycle control, tumor development, and even sleep induction. Additionally, the work has led to advances in determining the structural biology of signal transduction, and the molecular basis of protein recognition of nucleic acids. In the related area of biomolecular engineering, researchers have been able to build novel functions into proteins and RNA.

One of the key strengths of the department is the use of x-ray crystallography and NMR spectroscopy to determine three-dimensional structures and dynamics of key biological macromolecules. With a working draft of the human genome now complete, determining the three-dimensional structures of encoded proteins will become a critical factor in exploiting genomic data to obtain insights into biological function for improved drug design. The impact of the post-genomic era opens up new possibilities in molecular and structural biology. While scientists will soon have access to the complete list of all human genes, the determination of detailed structures is needed to accelerate therapeutic drug design. In the near future, scientists will be able to do for protein structure what has already been accomplished for genome sequencing, the next important step in the progress leading to the development of therapeutics and treatments.

Several members of the department are part of a consortium, headed by Ian A. Wilson, D.Phil., awarded a structural genomics pilot grant by National Institutes of Health to develop new technologies for high — throughput structure determination to enable scientists to obtain better insights into protein functions, their mechanisms of action, and a superior approach for designing new interventions — creating small molecules that inhibit their actions.

The department is large, with more than 50 full-time faculty members and more than seven times as

many supporting staff. In the post-genomic era, the methods for producing gene structures will increase in efficiency. Today, the process of mapping a particular protein to elucidate its structure and function can take from a few days to several months to complete. The power of the new technology will accelerate the research process dramatically, reducing the mapping process from weeks and months to a matter of days.

With all human gene sequences available, and new technologies like gene chips — thousands of pieces of DNA on a small glass biochip with special fluorescent readers for scanning the genes — scientists will soon be able to determine precisely which genes are expressed in various cells. One major task that lies ahead will be the mapping of related genes. For example, when a gene is activated, what is the effect? What other genes are activated with it? These maps of interacting genes and proteins will provide a critical understanding of basic human biological function at a much higher level than is currently available. The results will usher in a new era of molecular biology, in which the molecular pathways involved in all biological processes are understood in great detail.

Members of the department have already made considerable progress in the computer modeling of proteins and nucleic acids. A detailed understanding of the forces that not only determine the structure and function of proteins and nucleic acids, but also govern their interactions, can only be achieved through computer simulations. New advances have been made in computational modeling of protein folding pathways, while Charles Brooks, Ph.D., and his colleagues have made exciting progress in understanding the coupling between protein dynamics and enzyme catalysis. Others have made advances in the development of new computational tools for screening compound libraries for promising drug candidates.

Other studies continue to advance scientific understanding of molecular activity in important cellular processes, such as immune response, cellular signaling, and in control of the cell cycle. Future targets for structure determination include proteins and enzymes involved in bacterial and viral infection, antibiotic resistance, and the synthesis of homocysteine, a major risk factor for cardiovascular disease. Research continues on the molecular and biological characterization of feline immunodeficiency virus (FIV), a model for HIV. Scientists have made progress in understanding the regulatory mechanisms controlling FIV expression and mediating cell entry, as well as the development of inhibitors of key viral enzymes.

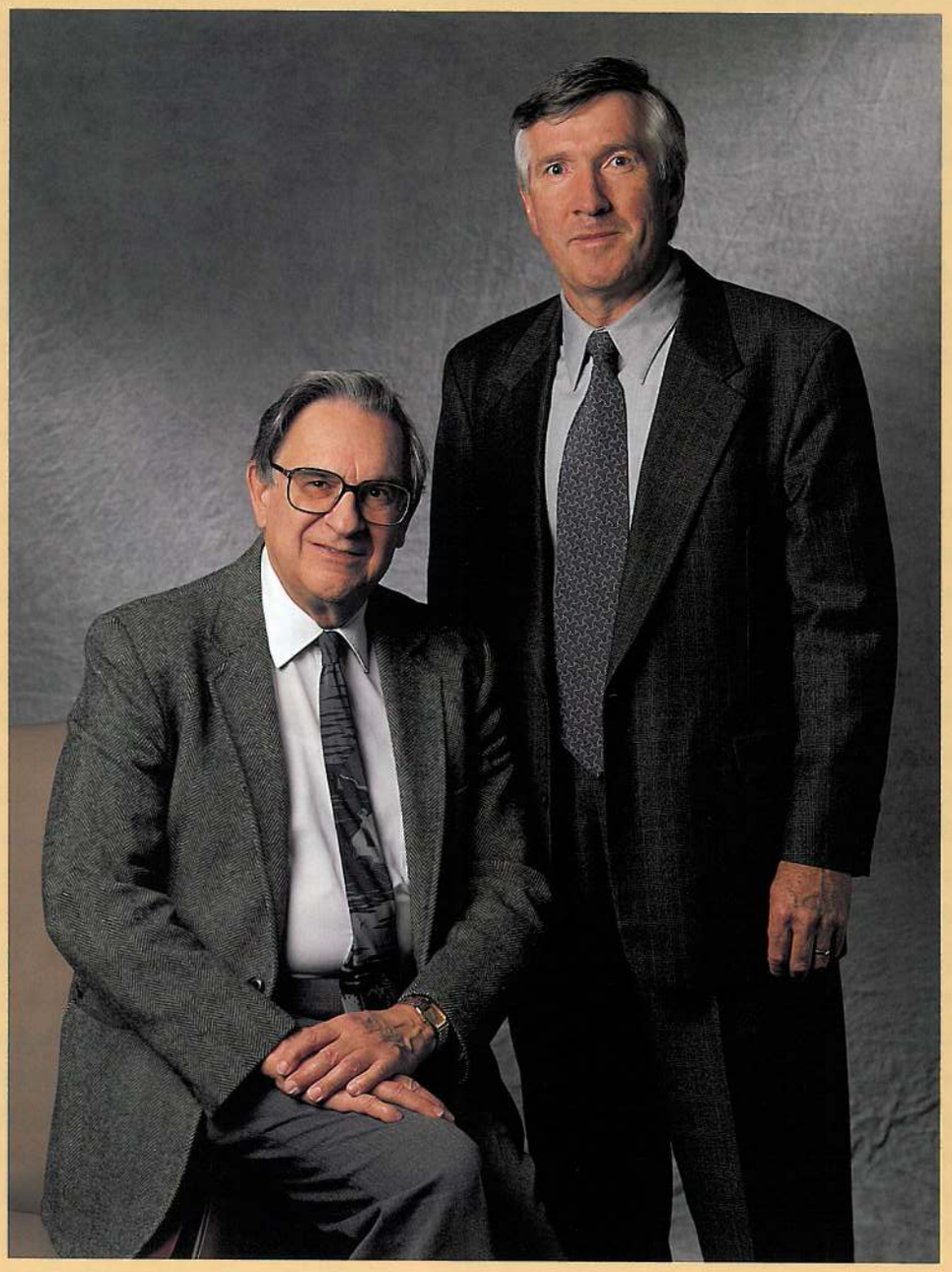
The tools of molecular genetics and structural biology are being used to build novel functions into particular metalloproteins — a protein and metal atom combined — that can specifically target any genome sequence, and that have potential applications in gene therapy. Peiching Sun, Ph.D., a new member of the department, has initiated research aimed at understanding the mechanisms of tumorigenesis. He has developed a novel technology to isolate genes involved in metastasis and tamoxifen resistance in breast cancer.

At the dawn of the new millennium, molecular biology remains a field of enormous opportunity and excitement. The scientists in this department have taken advantage of powerful new technologies to advance their understanding of fundamental biological processes at the molecular level. Their discoveries will ultimately be translated into new advances in biotechnology and medicine. ■

Molecular and Experimental Medicine

Ernest Beutler, M.D., Chairman

Science is incremental. While very few major discoveries are made in any single year, programs in the Department of Molecular and Experimental Medicine continue to make exceptional progress in advancing knowledge of biomedical science. This is not a clinical department, and although a number of its faculty members have significant clinical experience, relatively few continue to see patients. Nonetheless, among the departments at TSRI, this is closest to clinical medicine, and much of the work consists of translating basic laboratory work into clinical applications. The department also has responsibility for the General Clinical Research Center. This ongoing grant from the National Institutes of Health provides a clinical study unit within the Green Hospital, defraying the expenses of maintaining a staff, a core laboratory, and the ancillary costs of doing research. Today, the faculty consists of approximately 50 full-time scientists working with a total staff of 350.



Ernest Beutler, M.D.
Chairman
Department of Molecular
and Experimental Medicine

Peter E. Wright, Ph.D.
Chairman
Department of
Molecular Biology

One approach to improving medical care is to better understand important diseases, their natural history, and their response to treatment, thereby trying to devise new, more effective therapies with which to treat patients. Currently, members of the department are collaborating with Kaiser Permanente, one of the nation's largest health maintenance organizations, in a large study of the epidemiology of hemochromatosis, the major hereditary form of iron storage disease. Hemochromatosis is a metabolic disorder in which excess deposits of iron occur in the liver, pancreas, and other organs. Among other manifestations that may result are cirrhosis of the liver, diabetes and cardiovascular diseases. Already, a database of health information and DNA samples from nearly 30,000 patients have been assembled. Although it was originally thought that most people with the mutation that causes hemochromatosis were symptomatic and suffered a high mortality rate if untreated, the results of these studies to date show that very few manifest the disease. Most who are homozygous for this genetic mutation seem to enjoy a normal life span. This study may lead to rethinking the cost/benefit of screening normal populations for this disease and of the importance of its early treatment.

Another major program deals with hepatitis, a serious disease that affects millions of patients around the world. Under the leadership of Frank Chisari, M.D., a biomedical scientist who joined TSRI in 1973 as a postdoctoral fellow, the department has become a world leader in the study of hepatitis, especially of the body's immune response to the disease. Why are some patients able to rid themselves of the virus, while others continue to carry it and develop serious liver damage? Chisari and his team of researchers were successful in creating transgenic mice to study the body's immune response to the virus.

BROAD INTEREST IN CANCER AND ORGAN TRANSPLANTATION

The department also includes a wide-ranging research program on cancer. The laboratory of Peter Vogt, Ph.D., has been moving into several new areas, including developing innovative screening techniques aimed at cancer treatment. There has been a great deal of interest lately in studying the existing database of chemicals and antibody libraries for drugs that will help fight tumor cells more effectively. Vogt and his colleagues are engineering cancer cells to enable the detection of a response to any of tens of thousands of chemicals and antibodies available for study.

Organ transplantation is another important clinical approach to some forms of cancer as well as to kidney and heart disease. The studies of Drs. Daniel Salomon and Bruce Torbett have received substantial attention this year. In the field of xenotransplantation, the transplantation across species, pigs have been considered the most practical donors for man. The use of pig kidneys and hearts might allow many desperately ill patients who are waiting for a suitable human donor to receive a life-saving transplant. There are many hurdles to overcome before this could become a reality. Recently, however, there has been concern that a type of pig virus, a porcine retrovirus, might be transmitted to man. Salomon and Torbett recently demonstrated in studies published in the journal, *Nature*, that human cells can be infected by these viruses. At this point, further study is needed to determine whether or not this can produce tissue-to-tissue or even patient-to-patient infection.

The work on cancer also operates on an institutional level. ScrippsHealth, Scripps Clinic, and TSRI have worked together to create a new Scripps Cancer Center. The Center represents a close collaboration between clinical oncology and those TSRI scientists who conduct laboratory research. A goal of this program is to allow researchers to contribute more directly to the solutions they seek by moving useful laboratory techniques in cancer treatment quickly and seamlessly into the clinic through their close collaboration with the Center's clinical staff.

One of the long-term goals in the cancer center is to create a Good Manufacturing Practices facility to test drug candidates developed in-house. This will facilitate collaboration between the basic scientist and the clinician, making it possible to test new treatment modalities, while fulfilling government-mandated safety and regulatory requirements. An initiative to seek funding — both public and private — for this effort is under way.

Many members of the faculty of the department are world leaders in their field and their preeminence has been recognized by numerous awards and selection for service in important advisory bodies. The election of Bernard Babior, M.D., to the National Academy of Sciences brings the total number of members at TSRI

to 13, three of whom are members of the Department of Molecular and Experimental Medicine. ■

Neurobiology

Gerald M. Edelman, M.D., Ph.D., Chairman

While the Department of Neurobiology is small — with a complement of 30 staff members — its focus is the vast, and relatively uncharted terrain of the development of the vertebrate nervous system. Its scientists are particularly interested in the morphogenetic process — the growth of a particular organ or part of the body — as it applies to the interactions between functional groups of cells in the embryo, particularly as they change to form various tissue types within the central nervous system.

How does the nervous system wire itself? Is it controlled strictly by the genes? Can researchers create tools to manipulate gene expression more effectively? How does one begin with the single-dimensional genetic code at the embryonic stage and end up with a three-dimensional human being with billions of neurons working together to create thought, memory, and physical motion? The department continues to look for the answers to these fundamental questions by studying the links between genetic regulation and new ways of manipulating the processes that control such basic functions as cell division, cell movement and cell death. Working to find the answers are Drs. Bruce Cunningham, Kathryn Crossin, Frederick Jones, Vincent Mauro, Robin Meech, and several postdoctoral fellows.

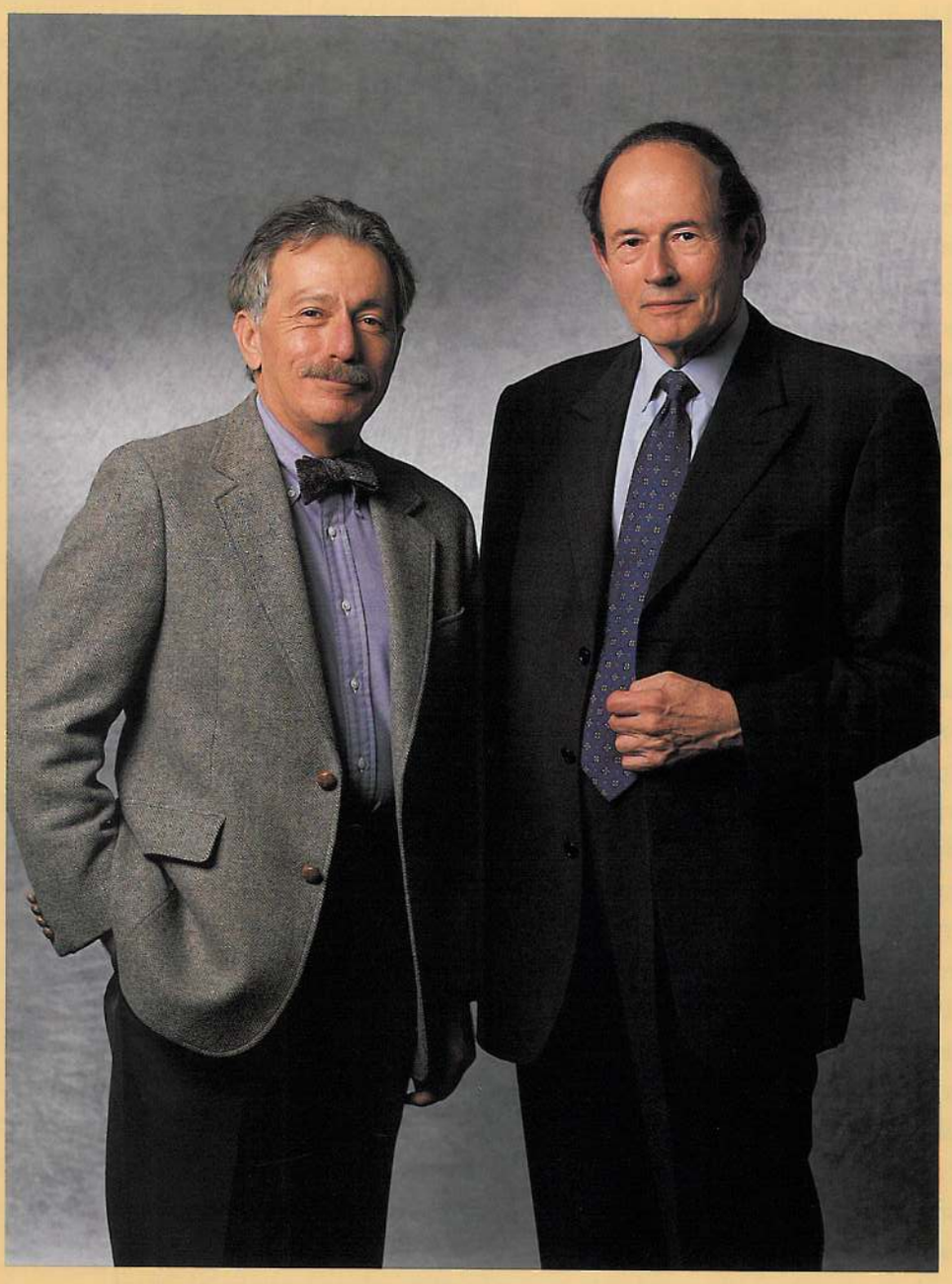
Simply stated, DNA produces RNA messages, RNA messages serve as templates for protein synthesis, and proteins induce changes in cells to produce various organ and tissue types that make up an organism. These scientists are interested in uncovering fundamental mechanisms of the transcriptional process — the way genetic information reproduces itself in RNA — and the translational process — the production of specific amino acid sequences (proteins) controlled by the genetic information in messenger RNA. RNA is created in the nucleus and exported out as messenger RNA and then, through the process of translation, expressed as proteins that cause changes in cell behavior. The control of these processes is much more complex and subtle than first anticipated.

Prime subjects for the research are cell adhesion molecules (CAMs), which were first discovered by the Edelman laboratory in 1978, and substrate adhesion molecules (SAMs). These two sets of proteins link cells together to form more complex tissue types and regulate cell proliferation, movement and differentiation. While humans share a majority of their genetic code with many other organisms, the real difference rests in the ability to switch certain genes on and off through various proteins, called transcriptional regulators. One of the group's major goals is to understand the influence of CAM and SAM binding on morphogenesis and gene expression, and how interaction with neural (N) CAMs and neural activity in general, may alter gene expression.

POTENTIAL APPLICATION IN GENE THERAPY AND BIOTECHNOLOGY

Recently, they expanded their study of regulation of gene expression caused by the interactions of messenger RNA and ribosomes, elements involved in protein synthesis that provide the translation machinery of the cell. Ribosomes recognize messenger RNA and their interactions lead to the synthesis of proteins. It was thought that the ribosome was recruited by the messenger RNA and scanned from one end to the other until the right starting sequence was reached. The work has shown that short sequences within the RNA messenger can also recruit the ribosome. When these short-recruiting sequences are linked together, a huge increase in protein expression results. This tremendous amplification of output may have potential application in gene therapy and biotechnology. Scientists also have shown that some messenger RNAs have other short sequences that regulate translation indirectly, that is, they seem to affect the efficiency of the ribosome recruitment sequences, acting as translational promoters or inhibitors.

Neural stem cells are the foundation of many other cells within the brain. Crossin discovered that by adding neural (N)-CAMs to rodent stem cells, the stem cells become transformed into neurons. Cellular therapy studies in other laboratories have begun to implant neural stem cells into the brains of mice with illnesses resembling Parkinson's disease, and have shown some limited success. The main problem has been that most of the implanted



Floyd E. Bloom, M.D.
Chairman
Department of
Neuropharmacology

Gerald M. Edelman, M.D., Ph.D.
Chairman
Department of Neurobiology

cells don't become neurons. In in vitro studies, when N-CAMs bind to rodent stem cells, a significant percentage — as high as 90 percent — become neurons. They are, in effect, biasing these stem cells toward differentiating into neurons, a bias that one day may point the way to novel treatments for a number of neurodegenerative diseases. Next year, the researchers have planned several in vivo experiments to implant these neuron-based stem cells into the brains of live rodents.

To date, research in the department has led to a deep reexamination of how all of these fundamental cellular processes are controlled and to the development of basic approaches to these processes that have practical significance. While the scientists are dedicated to basic research, the work with gene translation and transcription will have an impact on gene therapy and will allow fruitful clinical applications. ■

Neuropharmacology

Floyd E. Bloom, M.D., Chairman

During the past year, the research strategy of the Department of Neuropharmacology has remained fundamentally unchanged. Our scientists continue to focus on the ways in which infectious, environmental, and genetic influences lead to psychiatric, neurologic, or endocrine brain disorders. Only by studying these underlying mechanisms can researchers ever hope to devise effective treatments for these diseases.

The efforts of the departmental faculty are concentrated into five broad areas: molecular, cellular and systems neuropharmacology; neurovirology; neuroimmunology; psychopharmacology; and clinical neuropsychopharmacology. The common arc of these areas is their impact on two major human health problems: substance abuse — alcohol, psychostimulants, opiates, marijuana, and tobacco — and the effect of HIV infection on the central nervous system. With the appointment this year of Tamas Bartfai, Ph.D., and his colleagues in the Harold L. Dorris Center for Neurological Research, the work has been expanded into the field of neuropsychiatry.

This year's Nobel Prize in medicine was presented for research on signal transduction in the nervous system — how neurons speak to each other through chemical messengers in the brain. The primary work of the department resides in this area. Scientists here study the mechanisms of neuron synaptic communication to determine the difference between what is considered normal neuronal signaling and how it differs in AIDS patients or those who are dependent on alcohol, cocaine or morphine. The studies of these altered or damaged synapses will help to better define the nature of these diseases, and eventually lead to a better understanding of how to normalize the condition.

While HIV doesn't directly affect neurons, the disease causes great difficulty for patients' attention and memory. Our work shows that these problems are the direct result of the inflammation brought on by the lymphocytes coursing through the brain. This inflammation interferes with neuron signaling, slowing down the processes within the cerebral cortex, the thinking part of the brain. It is this critical area of cognition that is affected most significantly and very early on in the infection. Research in the department, particularly that of Howard Fox, M.D., Ph.D., has been instrumental in increasing understanding how HIV interferes with neuronal signaling. Using computers to monitor the brain's response to sights and sounds, scientists recognize that these pathways are affected in the early stages of the infection and are developing methodologies to reverse them with aggressive treatment.

The chemical communication between neurons is also significantly disrupted by drug use, but in different ways from that of HIV infection. Drugs such as cocaine and morphine act as natural neural transmitters, turning on what is known as the reward system within the brain. The neurotransmitters reward positive behavior by making us feel good afterwards — these are called reward circuits. A drug like cocaine simulates the actions of the reward circuits — and dependence develops because of these internal rewards, leading to repeated drug use.

In working with the neurobiology of drug and alcohol dependence, George Koob, Ph.D., and his colleagues have demonstrated the long-term effects of alcohol on the brain. Identifying the nature of the neuron transmitters that these drugs act on makes it possible to design new therapies that interrupt those effects, and blunt the influence of the drug.

Scientists in the department have great hope that their fundamental research into the neuropharmacology of diseases like AIDS and substance abuse will one day help produce new medications and new approaches to

alleviating human brain diseases. They can look back on a year of substantial progress in that fight, and continue to move forward into a new year full of opportunities. ■

The Skaggs Institute for Chemical Biology

Julius Rebek, Jr., Ph.D., Director

The Skaggs Institute for Chemical Biology is now in its fifth year, thanks to the extraordinary generosity of Aline and Sam Skaggs. Research is conducted at the interface of chemistry and biology with the long-term goal of finding cures for a broad range of diseases. Primary efforts are focused on organic synthesis, antibody catalysis, protein structure, RNA chemistry and molecular recognition.

The Skaggs Institute supports 29 principal investigators and more than 200 researchers. These scientists are also members of other departments including chemistry, cell biology, molecular biology, neurobiology and molecular and experimental medicine. The collaborations and synergy that link the research programs is one of the Institute's greatest strengths. As a result, its members have established a working environment that is genuinely diverse — multi-disciplined, multi-talented and recognized for its growing number of accomplishments worldwide.

Peter Schultz, Ph.D., Professor, Department of Chemistry, was appointed to The Skaggs Institute last year. A co-discoverer of catalytic antibodies, his breadth of interest and unbounded energy will continue to expand the genetic code, and apply a combinatorial approach to research in biological chemistry. The other co-discoverer of catalytic antibodies, TSRI President Richard Lerner, together with Subhash Sinha, have used these molecules to synthesize epothilones, promising chemotherapeutic agents.

A MODEL FOR INTERACTIVE RESEARCH

While the Institute's ability to sustain broad, long-term projects makes it unique, a more subtle accomplishment is its collaborative efforts between research groups. As a result, The Skaggs Institute has become a model for interactive chemical biology research. Some of the projects are practical, while others are focused on developing the next generation of molecules targeted against disease.

A number of innovative research activities define the growing spirit of the Institute and create a unique environment for the practice of chemical biology. The research on antibodies, for example, focuses on antibody catalysis — from developing new molecular sensors to detecting nerve gas agents to the production of antibodies in microalgae, which may eventually lead to the future development of human therapeutic and other important proteins.

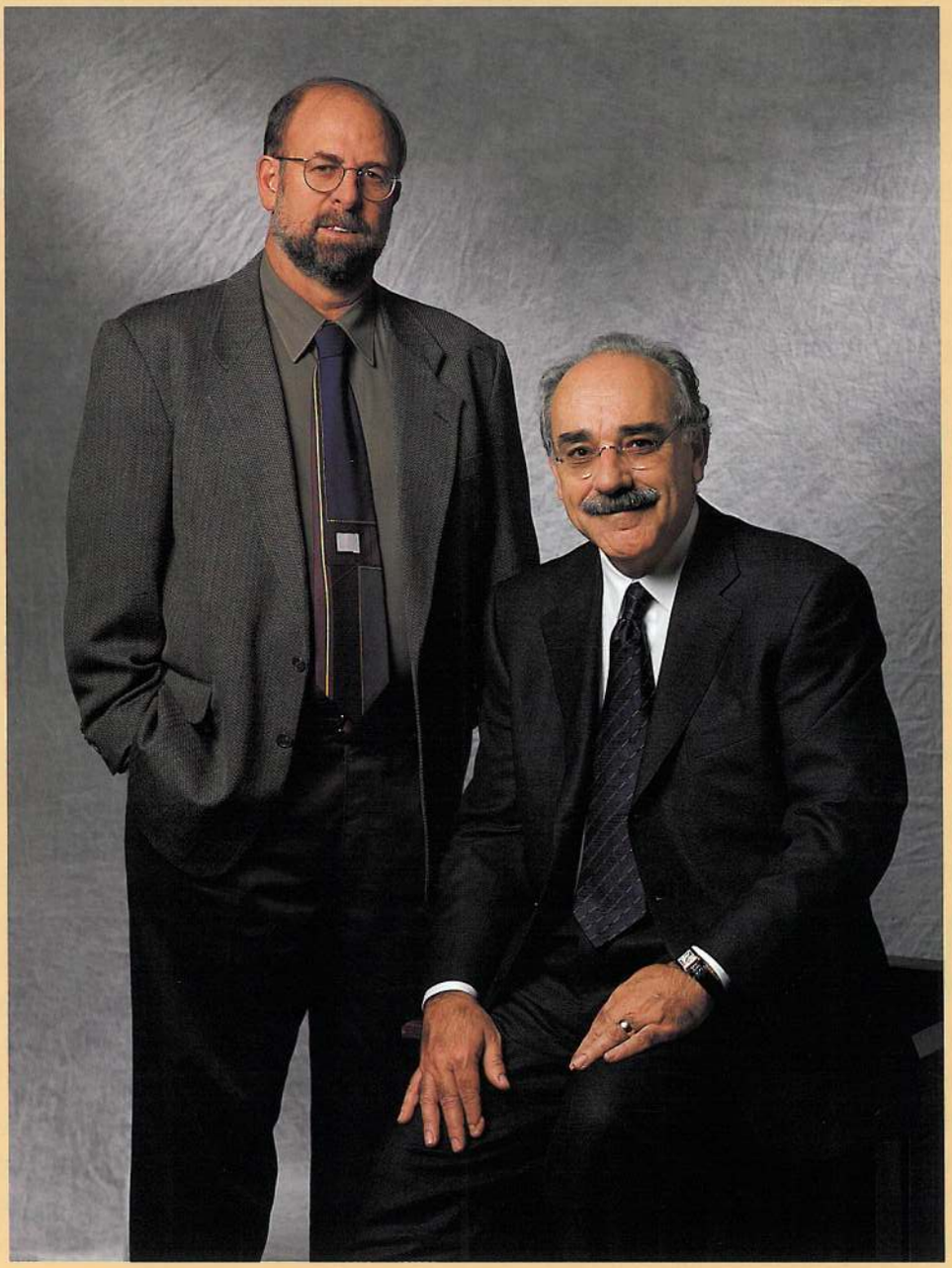
In chemistry, Chi-Huey Wong, Ph.D., was selected to receive a 2000 Presidential Green Chemistry Award presented by the U.S. Environmental Protection Agency, the director of the White House Office of Science and Technology and the president of the American Chemical Society. Wong's research centers on the use of enzymes for chemical synthesis, particularly molecules that bind to RNA, a rapidly emerging target for development of new antibiotics.

Another area of primary focus is cancer research. Last year, the anticancer agents epothilones and eleutherobins were synthesized, first as individual molecules and then as combinatorial libraries that allow scientists to quickly modify the chemical structure of these powerful agents. Combinatorial chemistry has captivated the Sharpless group; Professor Sharpless received the National Academy of Sciences Award in Chemical Sciences this year for these and other significant research accomplishments.

The organic chemistry of proteins is the area of research in Dr. Jeff Kelly's group, while Dr. Reza Ghadiri's lab confronts the frontier of chemical biology with its attempts to convert inanimate chemical reactions into animate chemistry. Ernest Beutler, M.D., Chairman of the Department of Molecular and Experimental Medicine, and his group study the regulation of apoptosis — programmed cell death — by various protein families.

Gerald Edelman, M.D., Ph.D., Director of the Neurosciences Institute and Chairman of the Department of Neurobiology, continues to study signaling mechanisms between molecules involved in cell adhesion, a process central to neural development.

In molecular biology, the focus continues to be the basis for genetic makeup. Topics of scientific investigation include uncovering the nature of the nucleic acid structure and why it is composed of particular sugars and bases, as



David J. Loskutoff, Ph.D.
Chairman
Department of
Vascular Biology

Julius Rebek, Jr., Ph.D.
Director
The Skaggs Institute
for Chemical Biology

well as the fundamentals of RNA — the chemical messenger that spreads the DNA code to the body's cells. In the area of RNA chemistry, Paul Schimmel, Ph.D., pursues his study of the rules of the genetic code, primarily the enzymes that recognize both RNA and amino acids. The self-assembly of RNA and its ability to act as a catalyst have been explored by Dr. Martha Fedor's group. The dynamics of intermediates in RNA folding has yielded to the studies of James Williamson, Ph.D., and his coworkers. The cleavage of RNA by DNA enzymes is one of the recent accomplishments in Dr. Gerald Joyce's group. In Dr. John Tainer's lab, the study of protein structure in the solid state has yielded the crystal structure of molecules involved in DNA repair, while structural changes accompanying genetic mutations in diseases such as ALS (Lou Gehrig's disease) are the focus of Dr. Elizabeth Getzoff's group.

The scientists' work this year, as in the past, demonstrates the greatest benefit that comes from the highly collaborative and synergistic environment of The Skaggs Institute for Chemical Biology — the ability to develop and sustain broad, long-term projects that go to the core of biological processes and human disease. ■

Vascular Biology

David J. Loskutoff, Ph.D., Chairman

Diseases of the coronary and cerebral arteries account for more than half of all deaths in Western societies, and the cost of managing vascular disease in the U.S. alone is more than $100 billion annually. The growing realization that vascular cells also play a critical role in the growth of tumors and a variety of inflammatory disorders suggests that the real cost of vascular disease may be even higher. The Department of Vascular Biology applies basic principles of cell biology, chemistry and genetics to study the development, structure and diseases of the vascular system.

A common goal of the work is to define the molecular basis for the very specific interactions between vascular cells and components in the blood and the extracellular matrix. These interactions are essential for normal cell growth, movement and differentiation, and represent the most fundamental processes in biology. Department members study how the interaction between specific integrins, and proteins in the cytoplasma and extracellular matrix of cells, regulate vascular cell growth and behavior. Integrins are a family of adhesion receptors on cells, and the focal point for cell matrix-interactions. When a ligand — an organic molecule that bonds with other molecules to form more complex structures — binds to its integrin receptor, it sets off a signaling mechanism inside the cell and creates a chemical reaction that causes the cell to change shape, move, etc. This chemical information is carried from the extracellular matrix through the integrin receptor into the cell, and results in changes in cell structure and function. Researchers here are working to unravel the molecular details and delineate the signaling pathways that govern integrin-mediated events in vascular cells.

They also seek a more complete understanding of the various roles of complex protease cascades in the control of vascular cell function. Proteases are enzymes that can degrade and destroy other proteins, including those present in the extracellular matrix and those that form blood clots. Those currently under investigation include the plasminogen activator system, matrix metalloproteinases, and cell death (apoptosis) proteases. A single molecule of a very specific protease, for example, can activate the entire blood clotting cascade, ending with the formation of hundreds of thousands of clot-forming prothrombin molecules, an elegant and exquisitely regulated process.

On the other hand, t-PA is a protease that can dissolve clot proteins and restore normal blood flow. Raymond Schleef, Ph.D., has employed genetic engineering to introduce t-PA into leukocytes, or white blood cells, and then insert them into rats. These protease-modified leukocytes go directly to existing blood clots in the rat circulatory system and dissolve them. This may be a new and more efficient way to deliver therapeutic proteases to sites of disease and injury.

Proteases also are frequently expressed in abnormal pathological situations. For example, certain types of invasive cells, including many cancer cells, use proteases to cut through tissue barriers during metastasis. Abnormal expression of certain protease inhibitors by vascular cells may increase the risk for heart attack under certain conditions, including obesity and type II diabetes, because the proteases that normally remove pathological clots no longer function. A lack of protease inhibition, however, can lead to bleeding problems due to the premature removal of normal clots.

REGULATION OF NEW BLOOD VESSEL GROWTH

Another area of research includes investigation into the mechanisms that regulate angiogenesis, the growth of new blood vessels, with a focus on integrins and proteases/protease inhibitors. These studies provide new insights into vascular diseases including tumor angiogenesis, arteriosclerosis, stroke, thrombosis, restenosis and hypertension, and bleeding.

During the past year, several scientists in the department have achieved recognition for their innovative research efforts and have attained increasingly prominent roles in national and international symposia. In addition, funding for vascular biology research at TSRI by the National Institutes of Health continues to grow at an accelerated rate.

Two new faculty members have been recruited to the department this past year, Drs. James Quigley and Heidi Stuhlmann. Quigley, formerly a professor in the Department of Pathology at the State University of New York in Stony Brook, brings with him a longstanding interest in the biochemistry and cell biology of proteases and their inhibitors in cancer and angiogenesis. Stuhlmann, from the Mt. Sinai School of Medicine in New York, is a mouse developmental biologist interested in the early development of the vascular system. She has identified a novel gene that appears to be important for vascular development in the mouse embryo.

The past year was extremely successful in terms of scientific accomplishments, the maturation of ongoing projects, and the development of new avenues of research. The department continues to organize the Vascular Biology Lecture Series and the Vascular Biology Retreat, thus providing an informal forum for investigators at TSRI who share common interests in proteases, integrins, and vascular development and disease. ■

Graduate Studies Program

Jeffery Kelly, Ph.D., Acting Dean

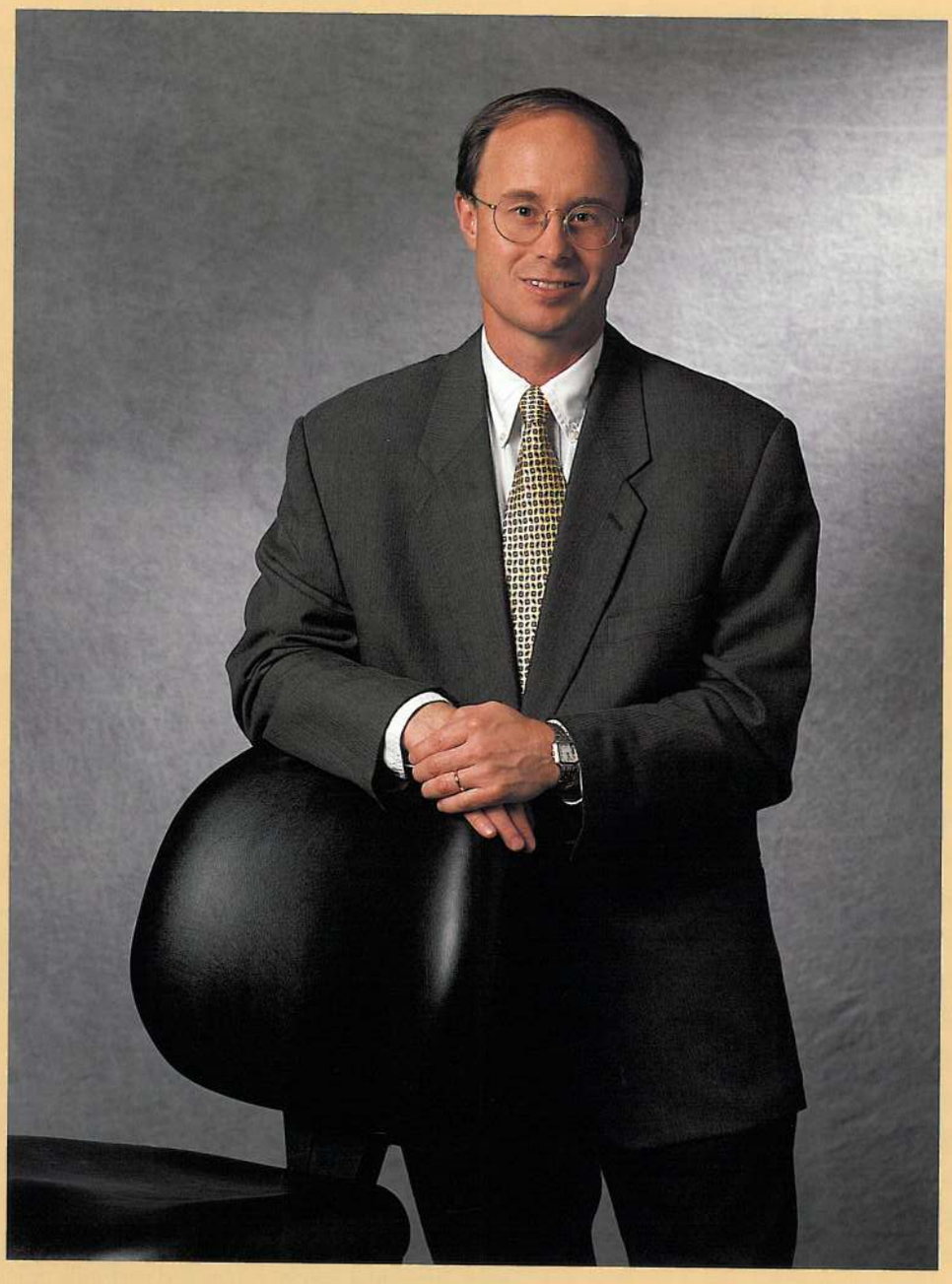
This year marks the 11th anniversary of the creation of the Graduate Studies Program at The Scripps Research Institute (TSRI). Although lofty goals were delineated at the inception of the program to measure its value and success, they have been exceeded by every measure, and the program has been integrated into the very fabric of the Institute. For the second year in a row, TSRI's graduate programs were ranked by *U.S. News and World Report* as among the most outstanding in the United States. The ranking was based on the results of a survey sent to department heads and directors of graduate studies at universities throughout the country.

The program ranked 8th in the top 10 Ph.D. programs in chemistry, a tie with Columbia University, and with The Rockefeller University tied for 10th place in the top 10 Ph.D. programs in biological sciences. When the programs were further categorized by specialties within a scientific discipline, TSRI ranked first in bioorganic and biophysical chemistry, a tie with the California Institute of Technology, and was judged to be 7th best in organic chemistry.

Further, The Western Association of Schools and Colleges (WASC) completed its reaccreditation process last year and conferred a 10-year accreditation on the program, subject to a mid-term review. This is the maximum term granted to any institution and a significant acknowledgment of the program's evolution and adherence to the highest standards.

Over the years, the Graduate Program has enhanced its competitive edge by recruiting highly qualified students from various disciplines and with varied scientific interests. In addition, time has brought a movement to a central position — the chemistry program has incorporated facets of the Macromolecular and Cellular Structure and Chemistry (MCSC) program into its curriculum and the MCSC program has taken appropriate elements from chemistry. The result has been a maturation of both programs. In addition, optional, short, independent courses have been incorporated into the MCSC program, providing special topics and methods training, such as in x-ray diffraction, statistical mechanics, special NMR techniques, immunology and virology. These courses provide for deeper forays into these topics for interested students and serve as supplemental studies to the core course work.

While research is the major component of Ph.D. programs in other institutions, the emphasis on research at TSRI is unusually strong, underscoring the synergy



Jeffery Kelly, Ph.D.
Acting Dean
Graduate Studies Program
Acting Vice President
Academic Affairs

between the missions of both TSRI and the Graduate Program. Students in the MCSC program finish the program as well-equipped problem solvers, with nearly 70 percent entering academia upon graduation and 30 percent being recruited to work in industry. Students in the chemistry track leave with the skills to become bioorganic or synthetic chemists in academia, where approximately 40 percent of the program's graduates obtain positions, or in the pharmaceutical and biotechnology industries, where 60 percent of the students are offered career opportunities.

This year, TSRI celebrated the conferral of doctoral degrees on 15 students. At commencement ceremonies held in May, Christopher W. Boyce, Robert M. Garbaccio, Yun He, Nicolas Winssinger, Jay P. Chiang, David S. Nirschl, A. Erik Rubin and Michael D. Burkart received a degree in Chemistry, and Andria Lee, Yuwen Wang, Melanie R. Nelson, Rachel L. Winston, Thomas K. Darlington, Amy B. Muhlberg, and Sudip S. Parikh received a degree in Macromolecular and Cellular Structure and Chemistry. Albert J. Eschenmoser, Ph.D., received the honorary doctor of science degree.

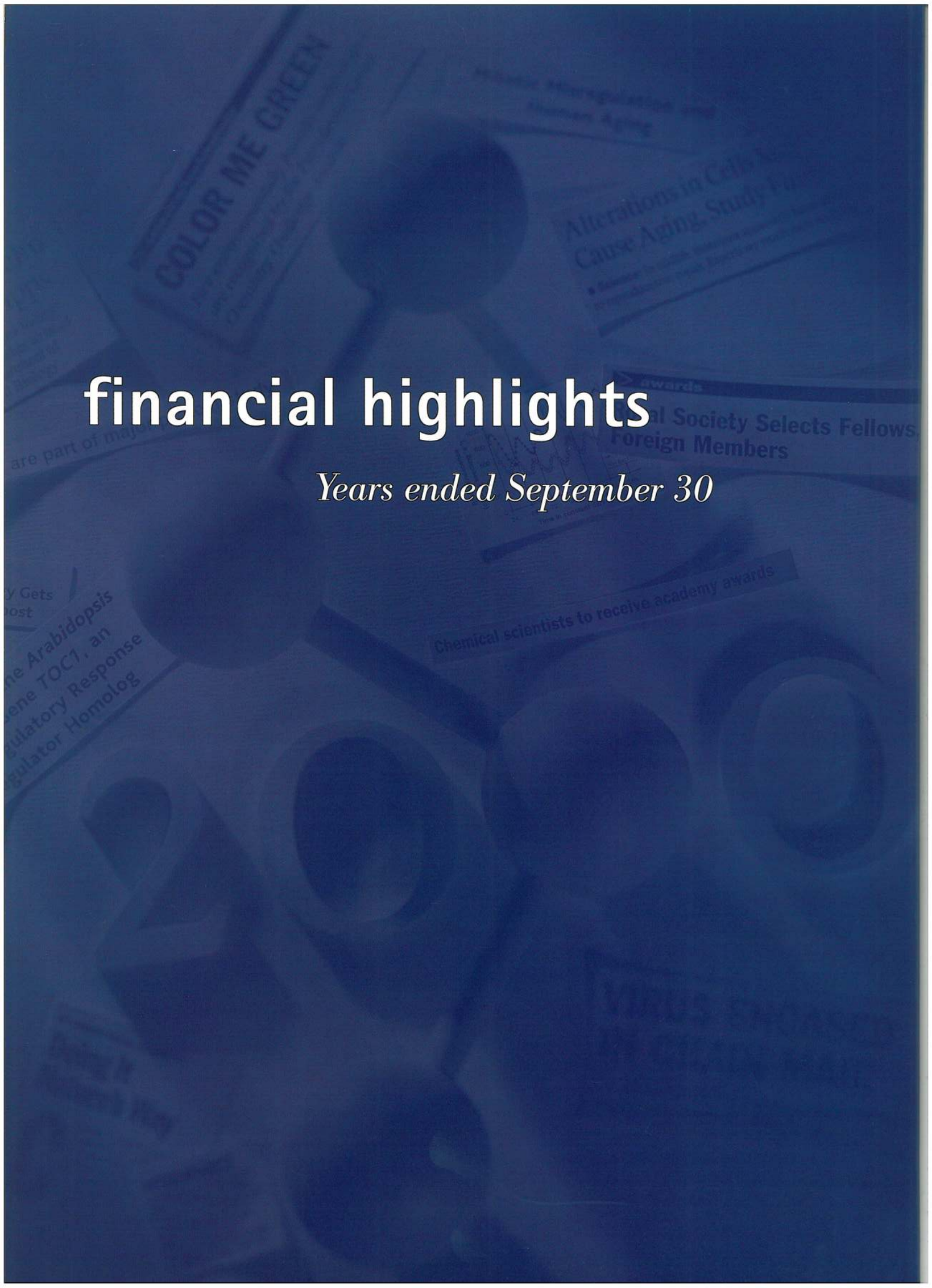
As in years past, an increasing number of students obtained financial support from a broad range of prestigious sources in government, corporations and private foundations, including: The Howard Hughes Medical Institute, National Science Foundation, La Jolla Interfaces in Science, Medical Research Council of Canada, American Heart Association, American Chemical Society, Heiwa Nakajima Fellowship, United Negro College Fund, National Institutes of Health, National Defense Science and Engineering Graduate Fellowship Award, Roche Award, Hewitt Award, Natural Sciences and Engineering Research Council of Canada, and Le Fonds pour la Formation de Chercheurs et l'Aide a la Recherche.

The Distinguished Lecturer Series hosts several prominent researchers at the forefront of the biological and chemical sciences at the Institute each year. In addition to attending formal presentations, students met with the scientists on an informal basis in a small group setting. Speakers who participated in the series this year included Kathlyn A. Parker, Brown University; William R. Roush, University of Michigan; John A. Katzenellenbogen, University of Illinois; Ken A. Dill, University of California, San Francisco; Gregory A. Petsko, Brandeis University, Alan Fersht, Cambridge University and Judith Klinman, University of California, Berkeley.

In an effort to make a contribution to the San Diego community, a group of 15 highly motivated graduate students has developed a curriculum for high school students, as well as a teacher training program under the auspices of TSRI's Science Partnership Scholars Program. Each program combines aspects of presentation, demonstration and experimentation. In addition, the graduate students serve as mentors to high school students, typically under-represented in the sciences, as they guide them through the college application process and provide counseling on careers in bioscience.

The Graduate Program held its annual retreat in September at the San Diego Paradise Point Resort on Mission Bay. Program components included two poster sessions and a series of 15-minute presentations by students. To further the interdisciplinary nature of the Graduate Program, presentations from both the MCSC and chemistry students were combined. The all day event was attended by approximately 175 students and faculty members.

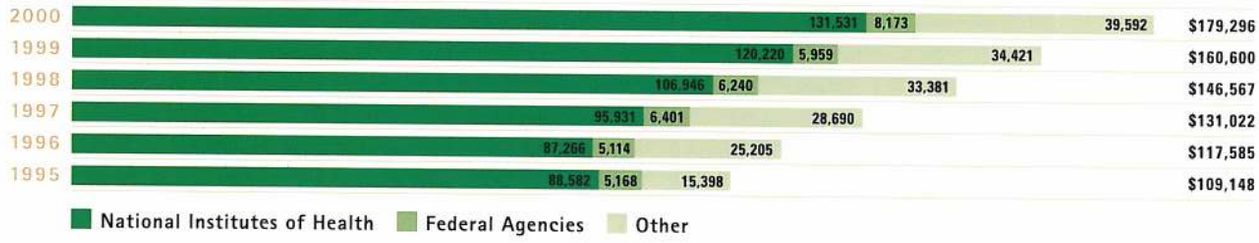
TSRI's faculty maintains a strong commitment to the Graduate Program, with more than 100 professors providing instruction to 74 students in the chemistry program and 70 students in the MCSC program. They provide the leadership and expertise necessary to maintain and enhance this program that serves as a reflection of the Institute's standard for scientific excellence. ■



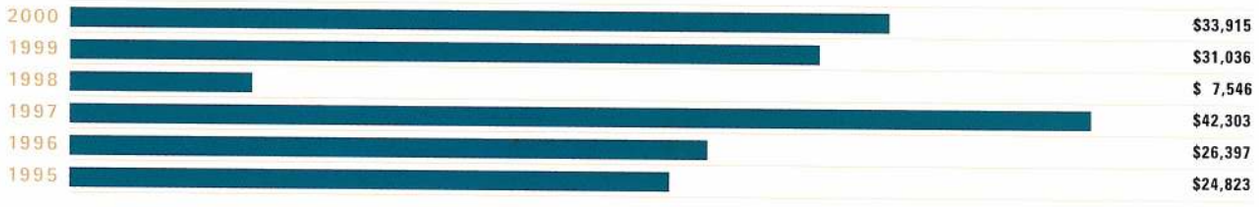
financial highlights

Years ended September 30

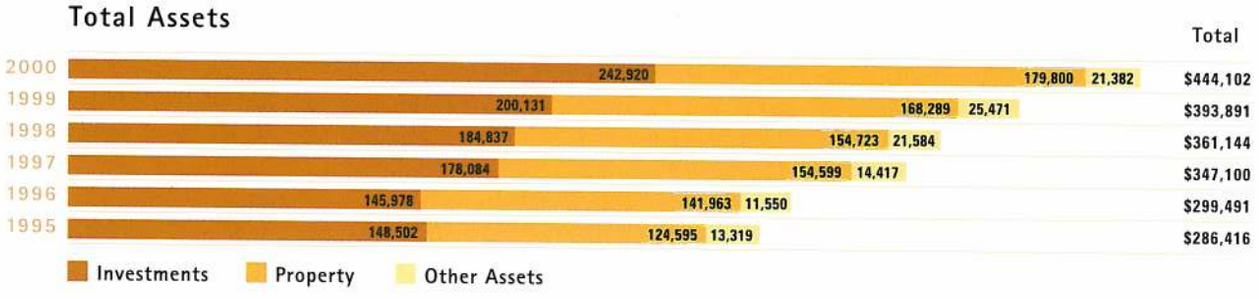
Sponsored Research



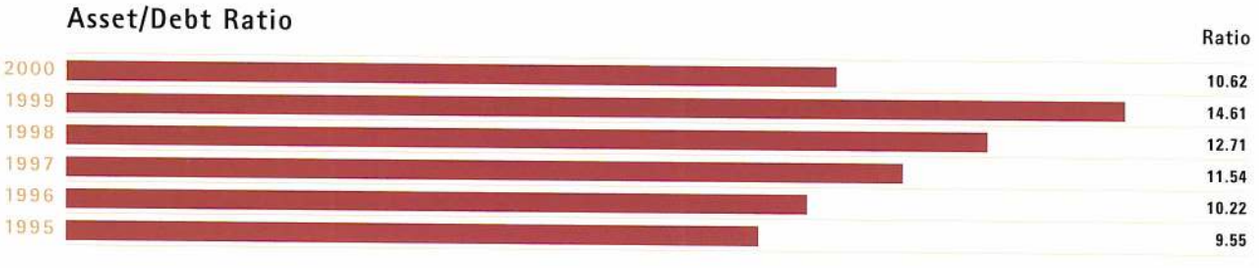
Net Income



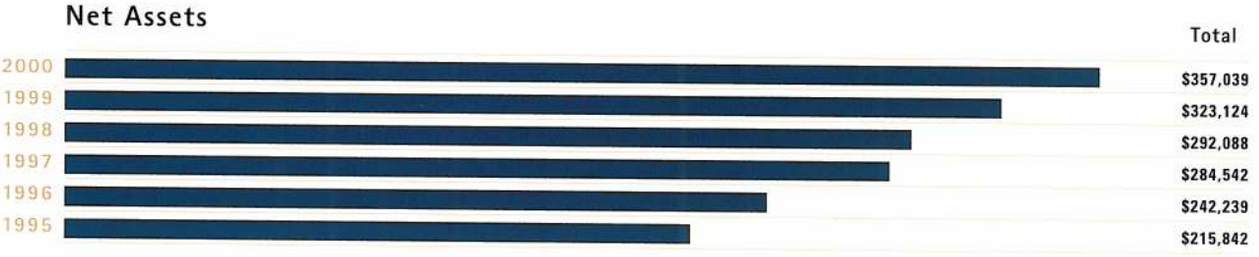
Total Assets



Asset/Debt Ratio



Net Assets



Dear Friends:

With this final issue of *Endeavor* for the year 2000, we have chosen to reflect upon the remarkable generosity, and faith, of those who have committed their personal support to further the endeavors of basic biomedical science at The Scripps Research Institute.

On the following pages are names of those who have donated gifts to support the Institute in the year 2000 as well as names of individuals who have informed us that they have named TSRI as a beneficiary in their estate.

We deeply appreciate this outpouring of private support for basic research at TSRI. Even more, we acknowledge that it is in many ways a lifeblood that assures continual renewal of our institution. By this I mean that private support provides the "venture capital" for our scientists to pursue new research opportunities that might otherwise be lost.

The Scripps Research Institute stands at the forefront of biomedical science today and is one of the most successful institutions in the country in competing for funding from the federal government and others for mainstream science. Mainstream science, however, requires a beginning; it is in the laboratories of both young and seasoned investigators that the unexpected often occurs which may lead to an entirely new field of endeavor. When this happens, we can only turn to the institution's private and discretionary resources, particularly unrestricted gifts, for interim support. Thus, these private funds actually "lever" much greater institutional support as the science that they are supporting matures.

There are many opportunities to participate in the endeavors at TSRI. They range from annual unrestricted giving all the way to naming of a department chair, a program, or an entire institute, as are outlined following this letter.

Finally, we are highlighting some of the individual gifts we have received over the years in sidebars on this and the following pages. As always, with all lists there is a risk of oversight. We are deeply grateful for those gifts which have supported individual scientists and programs essential to carrying forward our work.

We feel certain that private philanthropy will help TSRI to stay at the forefront of research that will provide the cures of tomorrow.

Please visit our web site at www.scripps.edu to learn more about TSRI and our programs.

With sincere appreciation,

Deeda Blair

Deeda Blair
Chair of the Development Committee

When we contemplate the tremendous impact that private philanthropy has had in thrusting The Scripps Research Institute (TSRI) to the forefront of biomedical science, certain words come to mind. Words like vision, tradition, foresight, entrepreneurial spirit, innovation, leadership, and legacy. Many supporters and friends of TSRI exemplify these virtues, and certain names stand out. On the following pages we have recognized some of these philanthropists.

Major Donors to the Scripps Research Institute

Special Acknowledgment

The following are those individuals and organizations who, over the years, have given $1 million or more in support of investigations at the Research Institute. We specially honor them and recognize their dedication to the advancement of medical science.

American Cancer Society, Inc.
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Anonymous (15)
Gordon M. Anderson Charitable Lead Trust
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Dr. and Mrs. Jack Avrack
Dr. Arnold O. Beckman and the Arnold and Mabel Beckman Foundation
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Mr. and Mrs. Leo Roon
The E.W. Scripps Family
Donald P. and Darlene V. Shiley
Aline W. and L.S. Skaggs
The Skaggs Institute for Research
Mrs. Betty L. Springer
Sam and Rose Stein Charitable Trusts
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Scripps Presidents' Council October 1, 1999, to September 30, 2000

The following list acknowledges the generosity of the many friends of The Scripps Research Institute who have contributed $1,000 or more during the past year or whose endowment funds have added substantial strength to our scientific programs and achievements.

$100,000 or more

American Cancer Society, Inc.
American Heart Association
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Arthritis Foundation
Donald E. and Delia B. Baxter Foundation
Burroughs Wellcome Company
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CaP CURE
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Leukemia Society of America
G. Harold and Leila Y. Mathers Foundation
Mr. and Mrs. John Jay Moores
National Foundation for Cancer Research
National Multiple Sclerosis Society
Novartis Agricultural Discovery Institute
Peggy Bruen Siegener
The Skaggs Institute for Research
Albert L. Weickert

$50,000–$99,999

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ARCS Foundation, Inc.
Mrs. Lela W. Cotter
Damon Runyon-Walter Winchell Cancer Fund
Merck & Co., Inc.
Gustavus and Louise Pfeiffer Foundation
Mr. and Mrs. Charles E. Scripps

Vision | **Occasionally in the ranks of philanthropists there emerge individuals who have unusual vision in tailoring their support in ways that will make a significant difference in the scientific endeavor far into the future. Among these individuals Sam and Aline Skaggs stand out as singularly visionary philanthropists. Their gifts, through the ALSAM Foundation and The Skaggs Institute for Research, have created the Skaggs Institute for Chemical Biology at TSRI, and The Aline and L. S. Skaggs NMR Building, and will support scientists for generations to come in unraveling the most difficult questions in life sciences.**

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Mr. Robert P. Scripps, Sr.
Marion Stafford

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Ruth Vernier
Mrs. Herbert W. Wehe, Jr.

$5,000-$9,999

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Tradition | **In the families of Jean and Keith Kellogg II, Burl and Bill Mackenzie, and Lois and Don Roon, there are long traditions of philanthropy. Jean and Keith Kellogg began their association with the Institution in 1977 and have over the years maintained a steady tradition of major support. Bill and Burl Mackenzie first became supporters of the TSRI mission in 1963 and have continued a generous level of support over nearly forty years. The Roon Family began supporting TSRI's parent institution in 1969 through major gifts by Leo and Anna Roon, Donald's parents. Don and Lois have continued that tradition to the present through both private gifts and the Roon Family Foundation. Donald Roon, Keith Kellogg, and Burl Mackenzie have all contributed generously of their time and leadership as well as, serving on both the Boards of TSRI and Scripps Clinic and Research Foundation.**

Foresight | In 1987, Sam and Rose Stein established a charitable lead trust which created an endowment of the largest gift that had ever been made to any Scripps organization to that date. With tremendous foresight, the Steins directed their endowment to the support of the Sam and Rose Stein Basic and Clinical Laboratories and the Department of Molecular and Experimental Medicine. It was from this department that the remarkable drug 2CdA, a near complete cure for Hairy Cell Leukemia, was discovered and developed.

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Entrepreneurial Spirit | Private foundations are often a source of the essential "seed" money for launching new ventures by both young and more experienced investigators. Without this type of support our scientists would not be able to pursue those "high-risk" but sometimes extremely promising new directions that result in scientific breakthroughs. Two foundations that have supported many promising new projects at TSRI over the years exemplify this entrepreneurial spirit. The Joseph M. Drown Foundation, under the direction of Milton Fillius, has provided funding since 1982 for such diverse research as monoclonal antibodies, protein folding, angiogenesis, a vaccine against cocaine addition, and a program to provide summer internships to high school students. The Donald E. and Delia B. Baxter Foundation, under the leadership of president Donald Haake, has supported projects since 1996 in the fields of cardiovascular disease, the chemistry of physiological states such as sleep, aging and neurodegenerative disease, the genetic basis of circadian rhythms, and anti DNA antibodies in diseases such as multiple sclerosis.

Innovation | **One most often thinks of innovation in scientific inquiry, but the spirit of innovation is also typified by the structuring of unique ways of being philanthropic. A shining example of the innovative spirit has been provided by John and Becky Moores, who saw the opportunity to turn their life long collections of coins and exotic cars into support for creating the Institute for Childhood and Neglected Diseases. The Moores' generosity and initiative in launching this new Institute have attracted many other donors who might not otherwise have considered unusual ways of giving.**

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Legacy | **Like the Skaggs family today, 75 years ago members of the Scripps family created the beginnings of a legacy that has followed down through the years. At the present time, second and third generation members of the Scripps family continue to be active philanthropists at TSRI and to lend not only their name but their long legacy of philanthropy in support of TSRI's mission.**

Commitment | From time to time the efforts of one individual will serve as a model of personal commitmenmt and dedication to a particular cause. Such is the case with Helen L. Dorris, President of the Harold L. Dorris Neuroscience Foundation. Her commitment to creating a neurological research center in a leading biomedical research institution came to fruition in 1998 with the Foundation's pledge of funds for establishing the Harold L. Dorris Neurological Research Center at TSRI. With Miss Dorris' support and participation, the Center for Neurological Research will continue to grow and flourish far into the future.

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Unrestricted Funds

The success of any research institution rests in its ability to identify promising new research programs in their infancy. Unfortunately, new programs generally do not qualify for federal grant support until they are fully developed. Similarly, young scientists who have not yet achieved prominence are also at a disadvantage in competing for grants. Their search for funds is apt to delay their work and inhibit them from striking out in new directions. Consequently, unrestricted gifts constitute one of our most valuable resources as they allow us to underwrite important new projects that might not otherwise receive funding.

Giving Opportunities | Gifts of all sizes are welcome. Contributions of $1,000 or more entitle a donor to annual membership in The Presidents' Council.

Institute for Childhood and Neglected Diseases

The new Institute for Childhood and Neglected Diseases at The Scripps Research Institute will apply the new molecular understanding of biology to address, reduce and successfully treat illnesses in two major categories – childhood diseases, including childhood cancers, and neglected diseases that effect populations primarily in developing countries.

The time has come to apply the burgeoning knowledge of genes to specific childhood and early-onset diseases. For a number of years, researchers have attempted to use new therapies like gene therapy against many of these diseases – cystic fibrosis and muscular dystrophy, for example, and certain forms of cancer. Unfortunately, none of these efforts has led to consistent success. But in each case, there is reason to believe that the work done thus far has laid the groundwork for approaches that will succeed. And in other cases, such as autism, scientists are only now uncovering genetic clues that might lead to better treatments.

The majority of the world's population lives in developing countries, and has yet to reap the benefits of the genetic revolution. But that is about to change and The Scripps Research Institute will accelerate the process. As biologists have begun to learn how human genes function, they also have begun to investigate the genes of parasites and other disease-causing organisms. The new Institute for Childhood and Neglected Disease is prepared to build on TSRI's previous successes, and will use the latest advances in biology to help vanquish parasitic diseases.

Giving Opportunities | Naming opportunities are available as follows:

Building	$5,000,000
Science Center	$3,000,000
Floor *(2 available @ $1 million each)*	$1,000,000
Director's Chair	$2,000,000
Institute Offices *(12 available @ $100,000 each)*	$ 100,000
Visiting Professor Office	$ 100,000
Conference Room	$ 100,000
Laboratory *(18 available @ $50,000 each)*	$ 50,000
Unrestricted/Principal Investigator *(12 available @ $500,000 each)*	$ 500,000
Senior Research Fellowships *(2-year fellowships)*	$ 150,000
Endowed Research Fellowship	$1,250,000

Faculty Chairs

An endowment gift to establish a named faculty chair at TSRI is one of the most meaningful and lasting gifts available to the private donor. Such a gift perpetuates the donor's philanthropy by creating a permanently funded position, named by or for the donor, which may be occupied in succession by major figures in the world of biomedical science. The benefits far outlast the life of the donor, and will be enjoyed by successive generations of family members.

Giving Opportunities | A commitment of $1,500,000 will establish a senior faculty chair bearing the name of the donor or loved one. A commitment of $2,000,000 will establish a named faculty chair to be occupied by a Dean, Director or Department Chair.

Senior Research Fellowships

Sometimes the implications for discoveries in basic research are unknown. Often, though, discoveries by geneticists, neuroscientists, immunologists and other basic scientists become the foundation for the most important breakthroughs in medical treatments and diagnostic technologies.

A gift to fund a senior research fellowship provides a scientist with the opportunity to pursue new directions that would have been otherwise left uncharted and could possibly lead to better therapeutics and medical advances. Funding a senior research fellowship would also be a great way of participating in one of the great scientific adventures of our time.

Giving Opportunities | A commitment of $75,000 or more will establish a senior research fellowship that supports the work of a faculty member or a senior scientist for one year. A gift in the amount of $1,250,000 or more will endow a senior research fellowship ensuring the ongoing funding of a scientist's research work or initiative.

Harold L. Dorris Neurological Reseach Center

The Harold L. Dorris Neurological Research Center was founded in 1999 as the result of a major naming gift and long-term commitment by the Harold L. Dorris Foundation under the direction of Helen L. Dorris.

The Center is bringing a dedicated effort to conducting research and education into neurological disorder, including schizophrenia and Alzheimer's disease, as well as advancing knowledge of the process of aging of the brain. The Center has attracted an international cadre of brain scientists, led by Tamas Bartfai, Ph.D. Dr. Bartfai is former head of central nervous system research at Hoffman-LaRoche in Basel, Switzerland, and former chairman of the Department of Neurochemistry and Neurotoxicity at Stockholm University.

The Center seeks contributions to supplement the original gift of $10 million to recruit additional senior faculty, establish named fellowships and create visiting professorship appointments.

Giving Opportunities | Contributions of all sizes are welcome. A gift of $1,500,000 will permanently name and support faculty chairs while a gift of $1,250,000 will establish named fellowships and a gift of $50,000 will establish a visiting professorship appointment of four months. Specific program funding in the range of $50,000 – $300,000 for new scholars is also a priority.

Graduate Degree Program

In 1989, The Scripps Research Institute (TSRI) established a Ph.D. program in Macromolecular and Cellular Structure and Chemistry. A second Ph.D. program in Chemistry was established three years later to focus on synthetic and bio-organic chemistry. Taken together, these programs provide an exceptional training opportunity in a unique learning environment for a select group of outstanding and intellectually diverse students.

We believe that The Scripps Research Institute's philosophy toward education, emphasis on individualized instruction, adherence to the highest scientific standards, and reputation for research excellence provide an unparalleled environment for advanced study and outstanding preparation for successful careers in science. Unlike other degree-granting institutions, The Scripps Research Institute does not charge tuition fees. Therefore, the institution must look to private contributions to provide permanent funding for the programs.

Giving Opportunities | Contributions of all sizes are welcome. A gift of $270,000 will permanently name and support an endowed graduate stipend while a gift of $18,000 will name and support a graduate stipend for one year. A commitment of $4,500,000 or more will entitle the donor to name the Graduate Program.

Summer Internship Program

In 1989 The Scripps Research Institute established a summer internship program for students from local high schools. This initiative was designed to give high school students, undergraduate students and middle and high school science teachers an intensive, basic hands-on science research laboratory experience.

Since 1993, over 200 high school students have participated in the Summer Research Internship Program. During the same time, nearly 25 science teachers have attended the program and 71 undergraduates from local colleges and universities.

At this time, the program capacity has grown to as many as 50 internship slots each summer. With the demand and popularity of this program in local high schools, one of the limiting factors on filling these slots is availability of funding. In addition, we have developed a teacher high school component, which will considerably enhance the teaching of sciences in the high schools themselves.

Giving Opportunities | Contributions of all sizes are welcome. A contribution of $2,500 supports the participation of one high school or undergraduate student in the program. A contribution of $5,000 supports the participation of one teacher in our Teacher Training Program or can fund a One Day Teacher Training Seminar on Contemporary Issues in Bioscience. A contribution of $100,000 or more can endow a program.

Endowments

The Scripps Research Institute seeks to enhance its endowment base from private contributions to provide ongoing income each year that can replace federal support. An endowment gift is one of the most meaningful and lasting gifts available to the private donor. The benefits far outlast the life of the donor, and will be enjoyed by successive generations of family members.

Giving Opportunities | A gift of $1,500,000 or more will permanently name and support a senior-level faculty position while a gift of $2,000,000 will establish a named faculty chair to be occupied by a Dean, Director or Department Chair. In addition, the Immunology Building can be named for a gift of $5,000,000 or more.

Other endowment opportunities exist throughout the institute's departments and centers. Specific programs such as the High School Student and Teacher Science Training Program can be endowed with gifts of $100,000 and up, and will be tailored to the donor's interests and wishes within the programmatic priorities of the institute.

Equipment Acquisition

TSRI enjoys one of the world's leading private computational capabilities with an array of computers, including a Cray supercomputer. Research is further supported by X-ray crystallography laboratories, high performance NMR spectrometry including a state-of-the-art 750 MHz instrument, electron microscopy, optical spectroscopy, a centralized DNA sequencing laboratory and a fluorescence activated cell sorting facility. Scientists are able to make new discoveries and advances in research with the help of modern technology.

TSRI scientists require state-of-the-art facilities and equipment to remain on the cutting edge of research and rapidly changing technology. New laboratory equipment and tools are constantly being developed to improve the efficiency and effectiveness of the scientists. Gifts of discretionary funding are needed to fund the continuous modernization of laboratories and equipment at TSRI.

Giving Opportunities | Gifts of all sizes are welcome. Contributions of $1,000 or more entitle a donor to annual membership in The Presidents' Council.

The Kresge Library

The present collection of the Kresge Library has its roots in the Medical Library established with the founding of Scripps Metabolic Clinic in 1924. At that time, the key reference tool used to identify relevant scientific and medical publications was the printed index. Since its founding, the Library has maintained subscriptions to three major indexes: Biological Abstracts which dates from volume 1, 1927; Chemical Abstracts which is complete from 1907 to present; and the print predecessors to today's Medline database which date from volume 1, 1916. Science Citation Index was added in 1975 to provide Scripps scientists and physicians with access to the unique advantages offered by citation indexing.

The Kresge Library is currently undertaking a major effort to expand access to these indexes electronically and making them available at the scientist's desktop. Private support for the Library is needed to take advantage of technological advances, and to purchase tools for students and faculty to manage the explosion of scientific and medical publishing. These tools are essential to the central mission of TSRI, which is to build on the existing base of knowledge and to rapidly disseminate new findings to the scientific community.

Gifts of discretionary funding are needed to fund the revamping of the Library. The Library's furnishings, specifically its study carrels and chairs have served generations of students and faculty and are in need of replacement.

Giving Opportunities | Gifts of all sizes are welcome. A gift of $100,000 or more will provide for the purchase of the electronic version of an index, thereby greatly expanding access. A contribution of $20,000 or more will refurbish the Library with new study carrels and chairs. Contributions of $1,000 or more entitle a donor to annual membership in The Presidents' Council.

Gifts to The Scripps Research Institute

Gifts to The Scripps Research Institute (TSRI) provide the assurance that our institution will continue its mission of striving for excellence in biomedical research. Unrestricted gifts are particularly useful as they can be applied to programs and areas of urgent need. Gifts may also be designated for specific purposes, such as research, educational programs, or equipment. They may also be made in tribute to or in memory of a relative or friend.

Gifts of Cash

An outright gift of cash is usually the simplest method of giving. It is not subject to gift or estate taxes, and you can deduct the gift amount from your federal income tax return up to 50 percent of your adjusted gross income. Should the gift total exceed your gift ceiling for that year, you can carry over the remaining deduction to succeeding tax years. This means that with careful planning, nearly every outright gift to TSRI can be fully deducted.

Gifts of Securities

Giving appreciated stocks or bonds is a superb way to show support for the institution. You can deduct the full fair market value of long-term appreciated securities, and avoid any tax on the capital gain. A gift of securities is deductible up to 30 percent of your adjusted gross income, with the five-year carry-over option. Under certain circumstances, however, you can choose to qualify for a 50 percent annual deduction by reducing the value of your gift by 100 percent of the appreciation in the contributed property-that is, to the cost basis.

Gifts of Real Estate

Almost any type of real property – a personal residence, a farm, a vacation home, a commercial building, or an undeveloped parcel of land – can constitute a gift. A gift of real estate can be made either outright or through other methods.

If the property has appreciated in value and is given outright, you will avoid any tax on the capital gain, reduce your taxable estate by the value of the gift, and receive a charitable contribution deduction for 100 percent of the fair market value of the property. Your actual income tax savings will depend on your tax bracket. You may deduct the value of the gift up to 30 percent of your adjusted gross income. Under certain circumstances, however, you can choose to qualify for a 50 percent annual deduction by reducing the value of your gift by 100 percent of the appreciation – that is, to the cost basis.

Gifts of Residence

The tax laws enable you to donate your personal residence or ranch and still live there for the remainder of your life. Furthermore, you can stipulate that your spouse may live there for his/her lifetime, or you may continue to live on the property for a set number of years. Either way, you will receive an immediate income tax deduction for the contribution.

The property does not have to be your primary residence – it can be a vacation or second home. Further, you do not have to reside on the property. You can also give stock in a cooperative apartment if the apartment is used as a primary residence.

The charitable deduction is less than the full value of the property and equals the value of the remainder interest given to us. There are also charitable deductions available for estate or gift tax purposes if the life interest is given to one or two individuals and the remainder interest given to charity.

Gifts of Undivided Interest in Property

You are allowed a charitable deduction for the value of an undivided portion of your entire interest in a property. This consists of a fraction or a percentage of each substantial right or interest in the property. The fraction must extend over the entire term of your interest.

Gifts by Bargain Sale

This entails your transferring ownership of an appreciated asset (real estate, securities and the like) to TSRI. In return, we would pay you an agreed-upon amount that is less than the full fair market value – usually your original cost. Essentially, you are selling your asset to us for less than its fair market value, so the transaction is part gift and part sale.

You might want to consider this method if the current value of the property exceeds the amount you wish to give or if it is not practical or economical to divide the property. You are entitled to a charitable deduction based on the difference between the sale price to us and the full fair market value. You incur tax only on the part of the appreciation attributable to the sale.

Gifts of Life Insurance

Sometime you may reach a point where life insurance no longer has the financial significance for your family that it once did. In that case, you may wish to make a gift of the policy to TSRI. There are two ways to do this.

First, you may make TSRI the owner of the policy. This allows you an immediate income tax deduction. If the policy is fully paid up, your deduction is equal to the replacement value of the policy unless that value exceeds the tax or cost basis. If premiums remain to be paid, the deduction is approximately equal to the cash surrender value. If you continue to pay the premiums on such policies, you will be entitled to a charitable contribution deduction. Or you may wish to contribute the amount of the premiums to us; we, in turn, could pay the premiums. As long as we are not under any obligation to pay the premiums, your contribution would be fully deductible.

Secondly, you also may name TSRI as the beneficiary of your policy. Since the designation is revocable it cannot be counted for any immediate tax savings. At your death, however, your executor may take federal estate tax charitable deduction for the entire amount.

Life insurance interacts well with other gift mechanisms. For instance, you can use all or part of your trust or annuity income to establish a irrevocable life insurance trust. The trust could purchase insurance on your life – perhaps an amount equal to the charitable gift – and you could name a spouse or child as the beneficiary. This way you can make a charitable gift and replace the assets with life insurance for the benefit of a loved one.

Alternatively, you could take all or a portion of the income for a set term of years and purchase a universal life insurance policy naming a family member the beneficiary. This is another excellent way to replace the wealth transferred to charity.

Life Income Gift

Another way to make a gift to TSRI is to transfer property (e.g., cash, securities, real estate) to the management of a trustee (for example, TSRI as an independent agent), and establish a life income arrangement. After the lifetimes of the beneficiaries, we receive the assets in the trust. Life income trusts provide many benefits to you as a donor: an income tax charitable deduction, a reduction in estate taxed, avoidance of capital gains taxes,

freedom from investment worries, and, of course, income for life.

There are several types of life income arrangements for different circumstances: unitrust, annuity trust, pooled income fund, gift annuity. Information about each gift arrangement is readily obtained from the Development Office at TSRI.

Gift in Trust-Wealth Transfer

A trust may be funded with property (e.g., cash, securities, real estate). The terms of the trust will provide for specific payments to TSRI for a number of years, after which the property is passed to a relative or friend of the donor. The donor receives sizeable estate and gift tax advantages, and TSRI immediately receives funds for its programs. This arrangement is called a lead trust.

Corporate Matching Gift

Many companies encourage philanthropic giving among their employees by offering to match an employee's gift with a corporate contribution. Donors interested in this opportunity should obtain the necessary matching gift form from their employer (usually the personnel office).

Gift by Bequest

One of the easiest and most common ways to make a gift to us is through a bequest in your will. The tax laws encourage bequests; consequently, a bequest is an excellent way to support our programs. Bequests work particularly well for those who are unable to make an immediate outright gift, but would like to aid us in the future. There are several types of bequests:

- Specific bequests take the form of an outright gift of money, securities or other property.
- With a residuary bequest, we can receive the residue of your estate after all other bequests have been made.
- A contingent bequest takes effect only in the event that all other bequests, for whatever reason, fail.
- A bequest may also take the form of a testamentary trust; to receive the tax benefits, however, the trust must either be solely for charity or be a qualified charitable remainder or lead trust.

When you make a bequest to us, your taxable estate is reduced by a 100 percent deduction for the amount of a cash bequest, or the fair market value of appreciated assets.

This deduction results in tax savings whenever the taxable estate – after other deductions – exceeds the amount offset by individual estate tax credits. Because the estate tax rate schedule is progressive, the larger the taxable estate, the greater the potential tax savings per dollar given.

For more information regarding any of these ways of giving, please contact:

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Benefits of Giving

For a one-time gift or cumulative gifts of the designated amounts you receive these benefits:

$10,000,000

- Founders status
- Continuing membership in the Scripps Presidents' Council

$5,000,000

- Benefactors status
- Continuing membership in the Scripps Presidents' Council

$2,500,000

- Patrons status
- Continuing membership in the Scripps Presidents' Council

$1,000,000

- Guarantors status
- Continuing membership in the Scripps Presidents' Council

$500,000

- Sponsors status
- Continuing membership in the Scripps Presidents' Council

$250,000

- Ambassadors status
- Continuing membership in the Scripps Presidents' Council

$100,000

- Advocates status
- Continuing membership in the Scripps Presidents' Council

$50,000

- Associates status
- Continuing membership in the Scripps Presidents' Council

$25,000

- Subscribers status
- Continuing membership in the Scripps Presidents' Council

$10,000

- Pacesetters status
- Continuing membership in the Scripps Presidents' Council

$5,000

- Supporters status
- Continuing membership in the Scripps Presidents' Council the year following a gift of $1,000 or more for any purpose

Scripps Presidents' Council

Founded in 1984, the Scripps Presidents' Council was created to serve two basic objectives: first, to provide a perpetual source of private resources for new and ongoing medical and research programs; and second, to provide a medium for sharing the excitement of our programs with those who invest in these undertakings.

Annual membership in the Scripps Presidents' Council is extended to individuals who contribute $1,000 or more in a given year. Those who have contributed $25,000 or more on a cumulative basis, or who make provisions for a bequest of $250,000 or more, receive membership benefits in perpetuity. Gifts may be earmarked for either specific research purposes, or left undesignated for use where the need is greatest.

Special privileges unique to the Scripps Presidents' Council are extended to all members:

- On request, personal assistance from a member of our Development Office regarding medical services at a Scripps Health hospital or informational needs
- A yearly report outlining the impact of your gift
- The Scripps Presidents' Council Special Event, an exclusive annual gathering.
- Special invitations to scientific briefings, receptions and lectures where fellow members meet to learn more about the vital work their contributions support
- Scripps Foundation Annual Report, which includes a listing of all Scripps Presidents' Council members
- A membership card listing the Scripps Health Information Line telephone number for immediate information concerning patient appointments and physician referral
- Selected press releases on topics of general interest sent to help keep all members informed about TSRI's newsworthy activities
- Scripps Foundation quarterly newsletter *update*, that discusses developments at The Scripps Research Institute, the latest clinical procedures available to our patients, and overall advances made at TSRI and Scripps Health
- TSRI Scientific Report, an annual report of scientific progress, awards received, and publications made by TSRI scientists
- Courtesy parking at all Scripps Health hospital facilities extended to all members
- And, of course, the satisfaction members receive from knowing they have personally contributed to the advancement of medical knowledge through their gifts.

If you are interested in joining the Scripps Presidents' Council, please contact:

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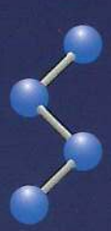

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