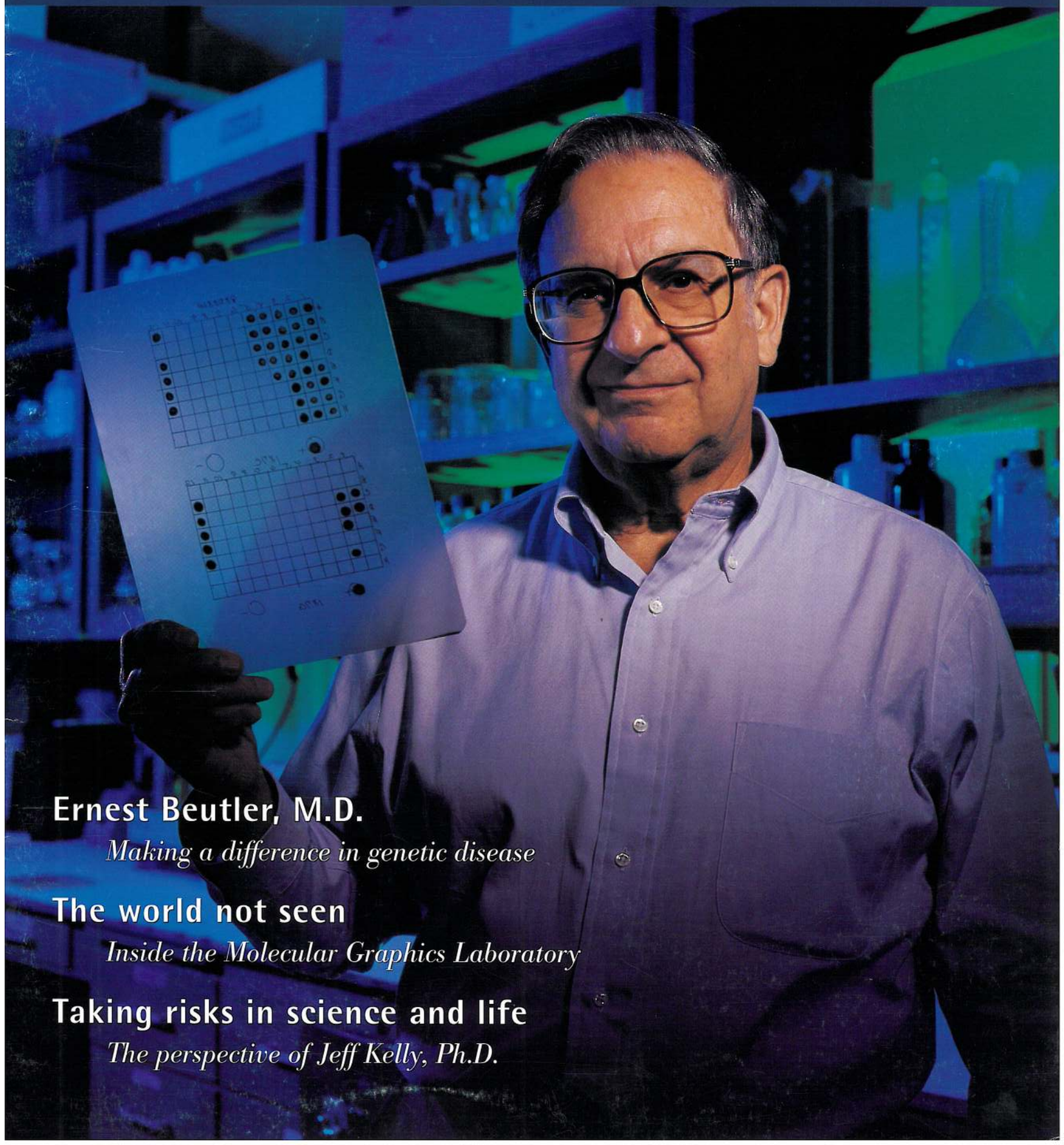
VOLUME ONE | NUMBER TWO

THE SCRIPPS RESEARCH INSTITUTE

Endeavor



Ernest Beutler, M.D.

Making a difference in genetic disease

The world not seen

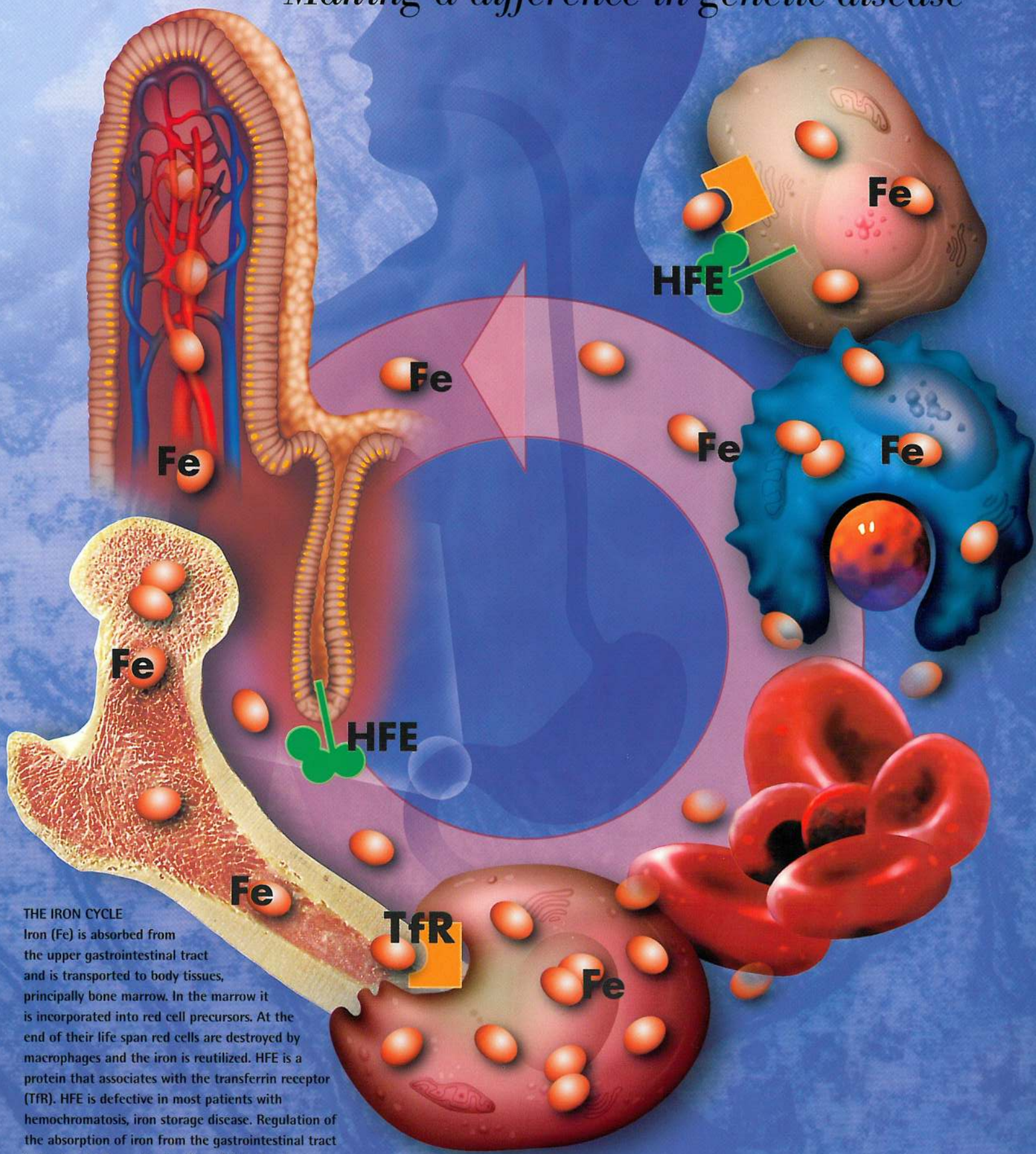
Inside the Molecular Graphics Laboratory

Taking risks in science and life

The perspective of Jeff Kelly, Ph.D.

Ernest Beutler, M.D.:

Making a difference in genetic disease



THE IRON CYCLE
Iron (Fe) is absorbed from the upper gastrointestinal tract and is transported to body tissues, principally bone marrow. In the marrow it is incorporated into red cell precursors. At the end of their life span red cells are destroyed by macrophages and the iron is reutilized. HFE is a protein that associates with the transferrin receptor (TfR). HFE is defective in most patients with hemochromatosis, iron storage disease. Regulation of the absorption of iron from the gastrointestinal tract is the key to the understanding of this disorder.

The very words "genetic disease" lead many people to the conclusion that nothing can be done — once a hereditary condition has been diagnosed, there is no remedy. But with many disorders there is reason for great optimism, says Ernest Beutler, M.D.

Chairman of the Department of Molecular and Experimental Medicine and Professor in The Skaggs Institute, Ernest Beutler, M.D., has spent a major part of his career studying the mechanisms that underlie many genetic diseases and searching for treatments based on a fundamental understanding of the disorder. Among these are hereditary anemias, storage diseases such as Tay-Sachs, Gaucher, and galactosemia (the inability to use milk sugar). One of his current interests is hemochromatosis, a common disease characterized by excess iron storage. This easily treatable genetic disease is likely to become a test case in the broad-based discussions currently underway regarding the use of genetic tests to screen the population for susceptibility to disease. And projects underway in the Beutler lab will be at the center of, and possibly help resolve, the debate about the benefits and risks of genetic screening.

Hemochromatosis is the most common genetic disease in people of European origin. It is a disease in which the body retains more iron than it needs and the excess iron can lead to cirrhosis of the liver, diabetes, arthritis, and damage to the heart. It is also one of the most easily treatable of all genetic diseases. The treatment is simple, drawing a unit of blood at appropriate intervals in the blood bank. Through blood donation the excess iron is removed from the body, thereby allowing patients to avoid the symptoms and to enjoy a normal life expectancy.

GENETIC MUTATION FOR HEMOCHROMATOSIS

The key discovery came in mid-1996. A biotechnology company, Mercator Genetics, discovered a mutation in a gene called HFE that predisposes people to hemochromatosis. The Beutler laboratory, along with many others, had been searching for this important gene. In confirming that the mutation was indeed the cause of the disease, Beutler says, "the really important thing is that the cause of most cases of this disease is now known. This has made it possible for us to move ahead rapidly with studies of how best to detect this very treatable disease and when to treat it." Beutler points out that hereditary hemochromatosis is an interesting disorder in which to study the interaction of mutations with each other and the environment in causing or exacerbating the symptoms of disease. At the same time, it is likely to become a testing ground for probing or even modifying society's attitude toward widespread genetic testing.

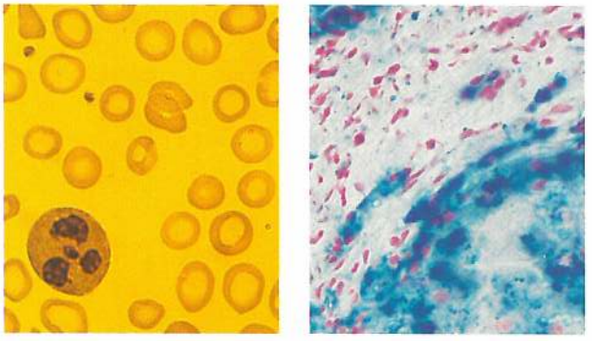
Hemochromatosis is detectable through conventional means, a blood test for serum iron and ferritin, sometimes followed by a liver biopsy. However, if patients are tested too early, the conventional blood tests and even liver biopsy may miss the disease. The availability of a genetic test makes it possible to determine, even from the time of birth, whether a person carries two copies of the altered gene. But will all such genetically predisposed individuals develop the disease? It seems fairly certain that some people might never suffer any symptoms. Consequently, it is not at all clear whether the performance of a genetic test on every adult would be helpful, or if it would unnecessarily raise anxieties and cause additional unneeded testing.

It is likely to become a testing ground for probing or even modifying society's attitude toward widespread genetic testing.

On The Cover: Ernest Beutler, M.D. inspects photographic film containing "dot blots." Where the film is exposed (black spots) a radioactive gene probe has found its sequence on the amplified DNA. This technique allows technicians to screen rapidly for the presence or the absence of a mutation in hundreds of samples.

GENETIC TESTING FOR HEMOCHROMATOSIS

By the end of 1996, two of the premier medical research and public health organizations in the United



To maintain good health, the body must meticulously control the amount of iron that it contains. If insufficient iron is present then iron deficiency anemia results. The red cells are small, pale and poorly filled with hemoglobin as shown in the microphotograph on the left. If there is an excess, as in hemochromatosis, iron (stained blue) accumulates in the liver and causes scarring as shown in the microphotograph on the right.

States, the Centers for Disease Control (CDC) and the National Human Genome Research Institute (NHGRI), considered it important to have experts address the issue of genetic screening. In March 1997 they convened a panel, which included Beutler and a number of other prominent physicians and research scientists, to discuss what course of action should be taken. The questions posed were: "Should there be widespread testing for hemochromatosis? And, if so, should it be based on measuring blood iron levels or should it be based on analysis of DNA?" The report, which has recently been published in the *Journal of the American Medical Association,* recommended against widespread genetic testing for hemochromatosis until more research had been conducted.

Working together with Dr. Vincent Felitti at Kaiser-Permanente in San Diego, Beutler has organized a study that should help answer these questions. Over the course of the next three years, the Kaiser-TSRI team will screen 60,000 patients for hemochromatosis. Each patient will, after giving appropriate informed consent, be given both a genetic test for the disease as well as the conventional blood tests. "In a population of this size, we expect to find about 200 patients with hemochromatosis. We will be able to establish comparative value of the new genetic test, on the one hand, and standard biochemical testing on the other." It will be the largest such screening study ever undertaken. The NIH and the CDC have provided funding of more than $4,000,000 for these clinical studies and the basic studies of iron metabolism that will be performed in the Beutler laboratory.

EXPLORING THE ORIGINS OF THE DISEASE

Beutler hopes that the screening project will also address some of the remaining mysteries surrounding the origin and course of the disease and the mechanisms by which the body normally absorbs iron. "We will evaluate iron intake, iron supplements, and the effect of infection with hepatitis viruses as well as other non-genetic factors," he says, "in order to examine the interactions between genetics and environment in this disease." Beutler and his colleagues have already shown that a second mutation in the HFE gene also increases the risk of developing hemochromatosis. When a person inherits one copy of the major mutation, called 845A, and a single copy of the other mutation, called 187G, neither of which is itself enough to cause disease, that person seems to have an increased risk, about 1.5 percent, of developing hemochromatosis. "What is different about these 1.5 percent of people from the 98.5 percent who do not develop hemochromatosis?" asks Beutler. The answer may lie in further mutations elsewhere in the iron transport pathway, or in various environmental causes. Between the Kaiser-TSRI study and the work in his own laboratory, Beutler intends to find out. In related work in his laboratory, Beutler and Pauline Lee, Ph.D., and their co-workers are studying further mutations that affect the likelihood

Over the course of the next three years, the Kaiser-TSRI team will screen 60,000 patients for hemochromatosis.

that a person will develop hemochromatosis. "Genes like the hemochromatosis gene function within pathways," says Beutler. "The pathway in which this gene functions transports iron. We are seeking mutations in other genes that function in the iron transport pathway, as well."

MORE EFFECTIVE SCREENING METHODS

The answer will be welcome, particularly to those who, like the CDC-NHGRI panel, want to determine the usefulness of screening. "By knowing more about auxiliary factors influencing whether someone actually develops hemochromatosis," says Beutler, "we may ultimately be able to make screening more effective." Beutler has high hopes that the upcoming screening study may provide information beyond that dealing with

hemochromatosis. If the study results show that genetic testing is helpful, this may help dispel public distrust in this important technology, distrust that Beutler sees as misplaced because it is based on a misunderstanding. It is important to provide many safeguards for genetic information in the case of late-onset, difficult, or impossible-to-treat diseases, such as cancer or Huntington's disease. "But in the case of hemochromatosis, the benefits outweigh the risks. It is about as clear cut an example as one can find, because the disease is so easy to treat," he says. "It would be throwing out the baby with the bath water to conclude that testing for hemochromatosis should not be carried out because screening for Huntington's causes unnecessary pain to those who receive the information. This issue needs to be considered one disease at a time."

Genetic diseases, Beutler points out, are "experiments of nature" that have taught scientists much of what they know about how the body functions normally. In the early 1960's a study of a red blood defect that causes anemia led him to propose, and then to demonstrate, that only one of the two X-chromosomes in the cells of women was active. In the 1980's the study of an inherited defect in immunity led Dennis Carson, M.D., working with Beutler at TSRI, to design a new drug, 2-CdA, that is now the standard treatment for some forms of leukemia and has proved very useful for the treatment of multiple sclerosis. Beutler points out that "the discovery of the HFE gene mutation in patients with hemochromatosis is a vital piece of the puzzle that we will try to put together to understand how the amount of iron in our bodies is normally controlled." ■

On the front lines of gene therapy

For years, Ernest Beutler, M.D., has been looking for better treatments for Gaucher disease, a sometimes life-threatening metabolic disorder caused by mutations in a gene that contains the genetic message for an enzyme. The lack of this enzyme, glucocerebrosidase, may result in the enlargement of the liver and spleen, bone fractures, and anemia. Physicians treat severe cases of Gaucher disease by infusing into a vein the missing enzyme, a medication which may cost as much as $500,000 a year. The hope for patients with Gaucher disease is to replace the mutant gene with a healthy gene that can produce as much enzyme as a patient needs. But replacing the gene is limited by physicians' ability to deliver the gene to the cells that can produce the enzyme. Attempts to perform gene replacement therapies including those that could treat Gaucher disease have all ended in failure. In most cases, a key hurdle has been getting the gene into adequate numbers of target cells and having it continue to function. Now, Beutler and graduate student, Danuta Balicki, M.D., are trying to surmount this obstacle. Their findings, cautions Beutler, may not lead directly to a treatment of Gaucher disease, but it could ultimately provide valuable insight into how healthy cells can be enticed into taking up genes. The target cells in Gaucher disease are macrophages, white blood cells that play a scavenger role. Based on favorable experiences of another research group, Beutler and Balicki attempted to use liposomes (little balls of fat) as a carrier system to ferry the gene into macrophages. But there was a problem: DNA has a negative charge. And to get liposomes into the macrophage, a specific component, phosphatidylserine, a fat molecule that is also negatively charged, might be helpful. But these negative charges would cause the carrier and the DNA to repel each other. "We need a bridge to bind the liposome and the DNA together," recalls Beutler.

That is when they decided to try histones. Because histones are positively charged, Beutler had a hunch that they might work to bridge the gap between DNA and liposomes. He reasoned that histones might work by acting as a glue between liposomes and genes. Moreover, they might help direct the genes into the cell nucleus because histones normally move to that part of the cell.

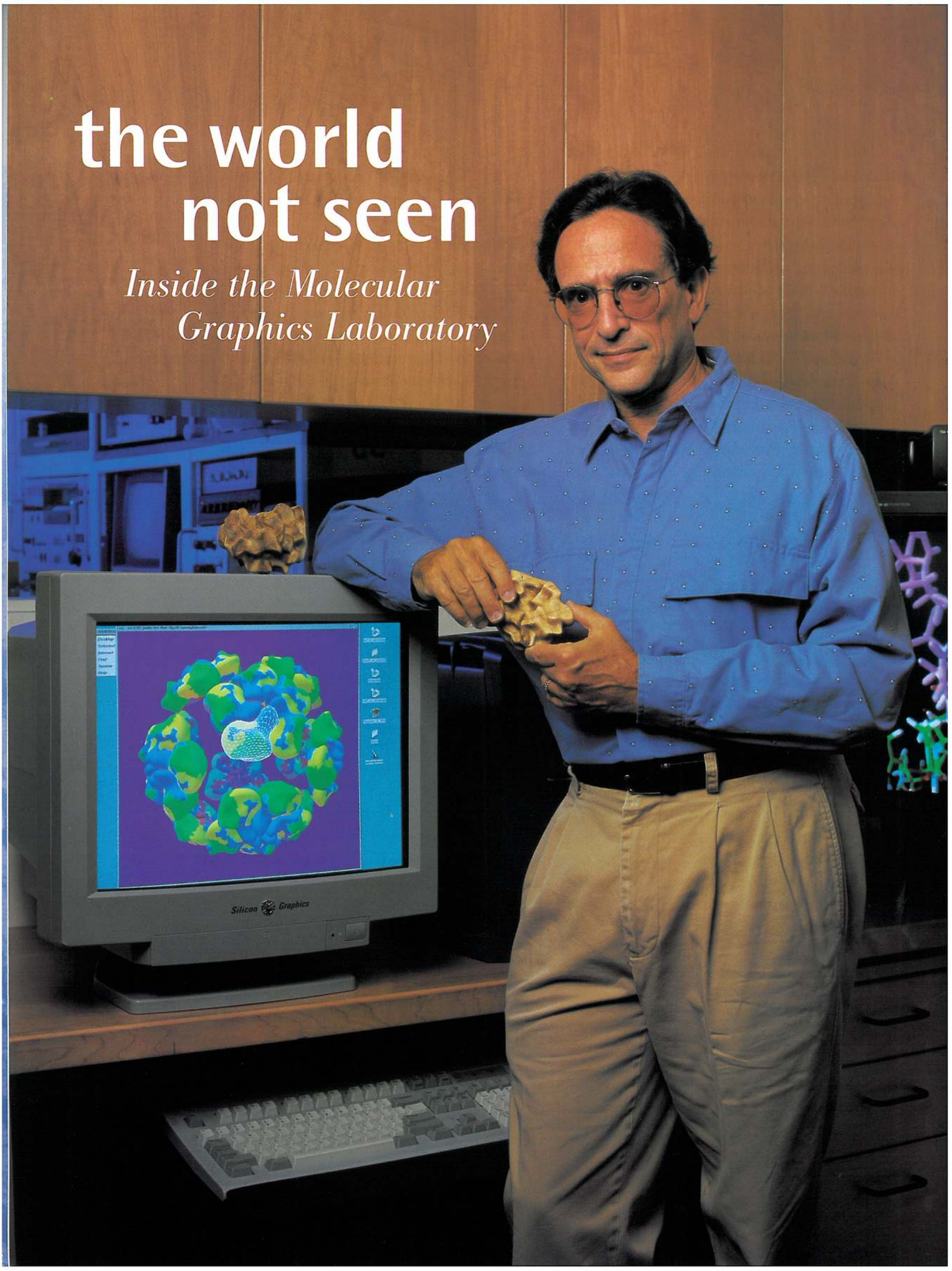
All the different classes of histones were tried, and none of them worked, except one. Just one histone protein, called H2A, had a dramatic impact on the uptake of DNA by the macrophages. "It was a thousand-fold difference." And it turned out that the liposomes were not needed at all. The effect was exerted entirely by the histone.

The results were published in the November issue of the *Journal of Molecular Medicine*. The implication for the treatment of Gaucher disease is that if the histone system can be refined so that it succeeds in bringing genes into macrophages, even for a relatively brief time, a valuable treatment may result. Gaucher disease is really different from other genetic disorders. "You do not have to correct the defect permanently," says Beutler. "Just correcting it every few months or every few years could bring the person back to perfect condition because the accumulated fatty substance would be removed." The end result may have wider implications: it may help get gene therapy back on track. ■

To study the penetration of genes into cells a "reporter" gene is used, the action of which can easily be detected. In this way, many different methods can be tested at the same time in a 96-well plate. The reporter shown here causes color to form. The more gene activity, the deeper the color.

the world not seen

Inside the Molecular Graphics Laboratory



Arthur Olson, Ph.D., is a Midwesterner by birth and a chemist by training so he views the day-to-day world around him with a practical eye that serves him well as TSRI's Director of the Molecular Graphics Laboratory, and Professor in the Department of Molecular Biology.

His day-to-day concerns involve keeping the lab moving ahead, and making certain that the work they do is on the cutting edge of molecular science, developing computational and computer graphic techniques to study and model three-dimensional biomolecular interactions. The global concept behind the Molecular Graphics Laboratory (MGL), Olson says, is to take "our knowledge of protein structures — the existing database is approaching 10,000 — and use them to understand biology. We develop computational tools to create complex structures from individual molecular components but with the atomic details still accessible. Our goal is not to understand everything about a cell but to understand the interactions within a cell. Then we can design drugs to capitalize on or modulate those interactions."

None of this explains the pure visual impact of the graphics produced by the lab or Olson's sustaining interest in projecting onto the visible world what he describes, paradoxically, as "the beauty of a world we can't see."

The illustration that graces the lab's web page is a good but minor example of that beauty, a dusky golden sphere, its surface thick with studs, surrounded by blue and purple wreaths that resemble Hawaiian leis. It is, more or less, your antibodies binding to a virus. As Olson points out, this particular particle is made of 180 protein molecules. Each one of those molecules contains between 3000 and 4000 atoms and as a practical matter, he knows the exact position of every single one of those approximately 720,000 atoms.

THE BEAUTY OF MOLECULAR STRUCTURE

But it's the look of this bit of biological flotsam that fully captures Olson's imagination: "There is something very special and very alien about molecular structures. They were designed by two billion years of evolution into a system called biology, a system we are just starting to understand. You can't help but be awestruck by its ingenuity and all of it is exceedingly beautiful. Even a virus — which can be something very dangerous to man — when you look at it, its symmetry is perfect and beautiful."

"Our goal is not to understand everything about a cell, but to understand the interactions within a cell."

The nexus of art and science that MGL represents takes a crosspollinating patchwork of expertise to sustain. Perhaps this is what Olson has in mind when he explains the dynamics of the people who work in the lab. Some are experts in x-ray crystallography — the process by which scientists determine the three-dimensional structure of molecules — and are superb visual artists as well; another has a degree in applied math but uses it for drug design; another is a Bell Labs computer alumnus deeply interested in physical chemistry.

Anyone of them could have gone the traditional path of a single discipline, he says, but somewhere their interests broadened into various interdisciplinary branches. Just like his did.

Facing Page: Professor Olson among the various forms of computer output from his laboratory. A high-end 3-D interactive computer workstation shows a model of poliovirus assembly. The video monitor shows some of the animations produced in the Molecular Graphics Laboratory depicting dynamic molecular processes, such as DNA transformations. Olson is holding a physical 3-D model of proteins produced from the computer.

This computer model of the poliovirus shows how the 60 basic subunits fit together to make the viral shell. Each subunit is composed of 4 protein chains – shown in different colors. Five subunits form each of the 12 pentameric faces of the intact shell.

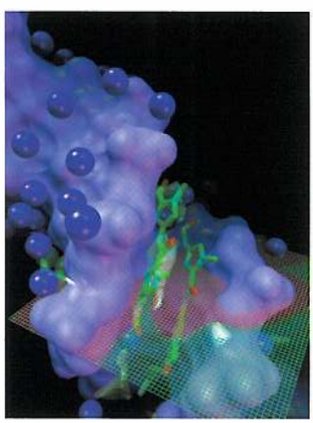
A more detailed view of the poliovirus surface showing how the individual protein chains of the 240 protein molecules interact to form the complete shell which protects the viral genetic material inside. The intricate hills and valleys of the viral surface can be seen in this type of visualization.

What they try to capture with the graphics — a computerized extension of scientific illustration, Olson admits — is to simplify and clarify an extremely complex entity so that the pictures represent in a very real sense the nature of the molecule. This is where the colors come into play. The colors used by these graphic visualization scientists are sometimes extravagant and end up making a statement all by themselves.

And a great many of them can be viewed on the lab's Web site (and downloaded as stunning wallpaper for your computer). These spectacular pictures range from the red spangled Christmas ornament look of one molecular surface model to the frothy pink and bright green harlequin design of another. Some are rich and seductive, like the deep red necklaces of a protein lattice model. Others are pure science fiction — the gridlike superstructure of another lattice model intertwined with glowing green and red cords of what appears to be a distinctly alien origin.

"When a larger audience begins to understand and appreciate science more, the better it is for science and scientists in general."

"The color is a good information channel," Olson says, "a way to use the computer to illustrate the qualities of an entity in a particular way. It's a scientific and artistic goal, using color to integrate information into a three-dimensional picture. These things aren't fantasy, remember. They're based on measurement and observation."



AutoDock is a program that can predict the interactions of drugs with target biological molecules, such as this new class of minor-groove DNA binding molecule. The DNA surface is shown in light blue, water molecules are shown as dark blue spheres, and the drug molecule is shown as the tube structure with atom coloring (carbons green, oxygens red and nitrogens blue). The grid and small cyan surfaces represent the energy of interaction between the drug and DNA.

He continues, "The question is deciding what's the most effective way to communicate, and aesthetics is part of that. People will take more time to examine an image if it's pleasing to look at. So there is an art to producing the images and the animations that we do. The people in our lab are willing to put time and effort into making something that looks as good as it is scientifically accurate."

The key to the lab's work is that they do good science. The graphics are a bonus for themselves as well as others — they're something they like to do. It's also another way of gaining recognition for the lab and for TSRI. Recently, the Santa Barbara Museum of Art asked Olson to contribute several lab graphics for a show on the interface of science and art. This artistic recognition may not have much impact on the lab's funding, but it does impact a broader audience. In addition, Olson maintains, it helps increase the public's appreciation of science.

"When a larger audience begins to understand and appreciate science more, the better it is for science and scientists in general," he observes. And science is what continues to move MGL forward.

THE IMPORTANCE OF MOLECULAR MODELING

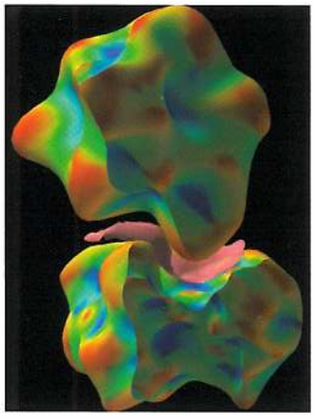
Molecular modeling will not, in the near future, eliminate animal or human testing, Olson explains, but as a science it has reached the level where it can produce important new drugs like the recently approved HIV protease inhibitors, a number of which were clearly products of a rational or structure-based approach. For Olson, these compounds are a genuine milestone in the evolution of pharmaceutical science, and their success puts to rest any criticism of the ability of rational drug design to deliver.

The lab has made its own unique contribution, a software tool called AutoDock. The program allows researchers to take lead candidate molecules and simulate docking those molecules to a target protein on the computer. This provides clear and detailed data about

the ability of a leading drug candidate to bind to a specific target without investing excessive laboratory time or financial resources.

"With AutoDock, we can look at potential drugs and evaluate them before the experimental work has to be done. We can also enhance and refine the drug binding process on the computer. AutoDock is very successful in a wide range of problems."

The lab also received funding to produce models of the evolution of drug resistance in some of those very same HIV protease inhibitors. Resistance to HIV evolves quickly in patients, and presents a real danger for those being treated. Without strict compliance, a mutant strain of the virus can emerge rapidly. The development of computational tools that can incorporate drug resistance in the process of drug design is important and will be even more critical in the future, Olson says.



Another area that Olson sees as important is education, and he would like the lab to participate in that as well. "We don't necessarily want to send our people into classrooms but use our expertise in the lab to prepare educational materials that students could download from the Net, for example. Kids are naturally curious about things, particularly this world that they can't see but that they hear so much about."

DESIGNING NEW MOLECULES

Beyond that, Olson would like to see the lab move in the direction of design, taking the knowledge they've gained to develop a true picture of life's molecular machinery and applying that to increasingly larger biological systems. His ideas here sound very much like an extension of the futuristic lab graphics.

"We want to design large protein assemblies that can perform particular tasks that may not necessarily have evolved in living organisms, such as self-assembling building materials with specific shapes and characteristics — smart materials that can transform themselves under certain conditions. We might even try to build computers using biology."

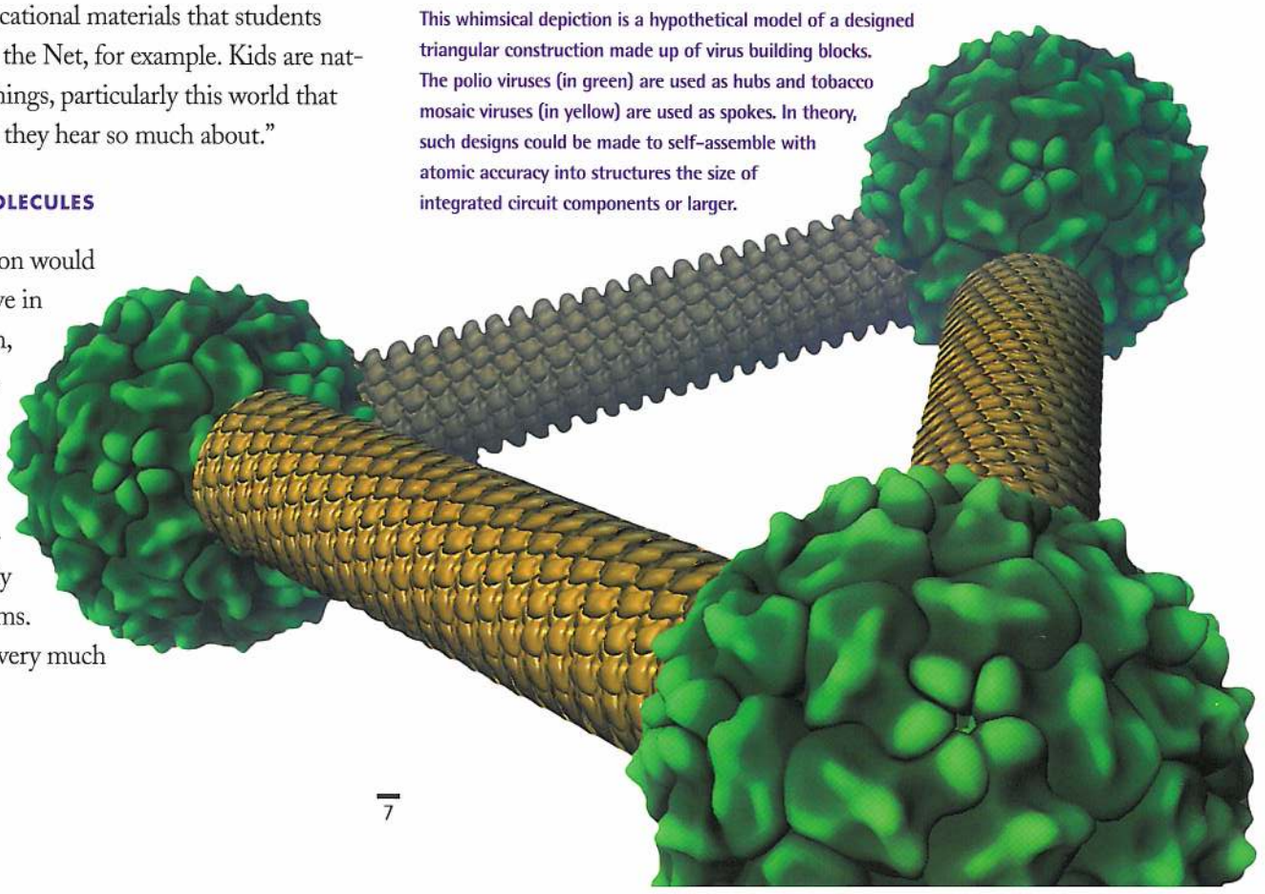
"We might even try to build computers using biology."

On one hand, Olson believes that the potential of this work is nearly unlimited — a new world of plenty and a higher living standard for people all over the world. On the other, he is practical enough to know the social and economic implications of this future vision, and that there will have to be a serious dialogue between science and society about how we want to deal with these things.

But all this is in the future. Right now, we have more than enough of the practical and the sublime — life saving drug discovery tools and strikingly imaginative pictures, all built on the world none of us can see. ■

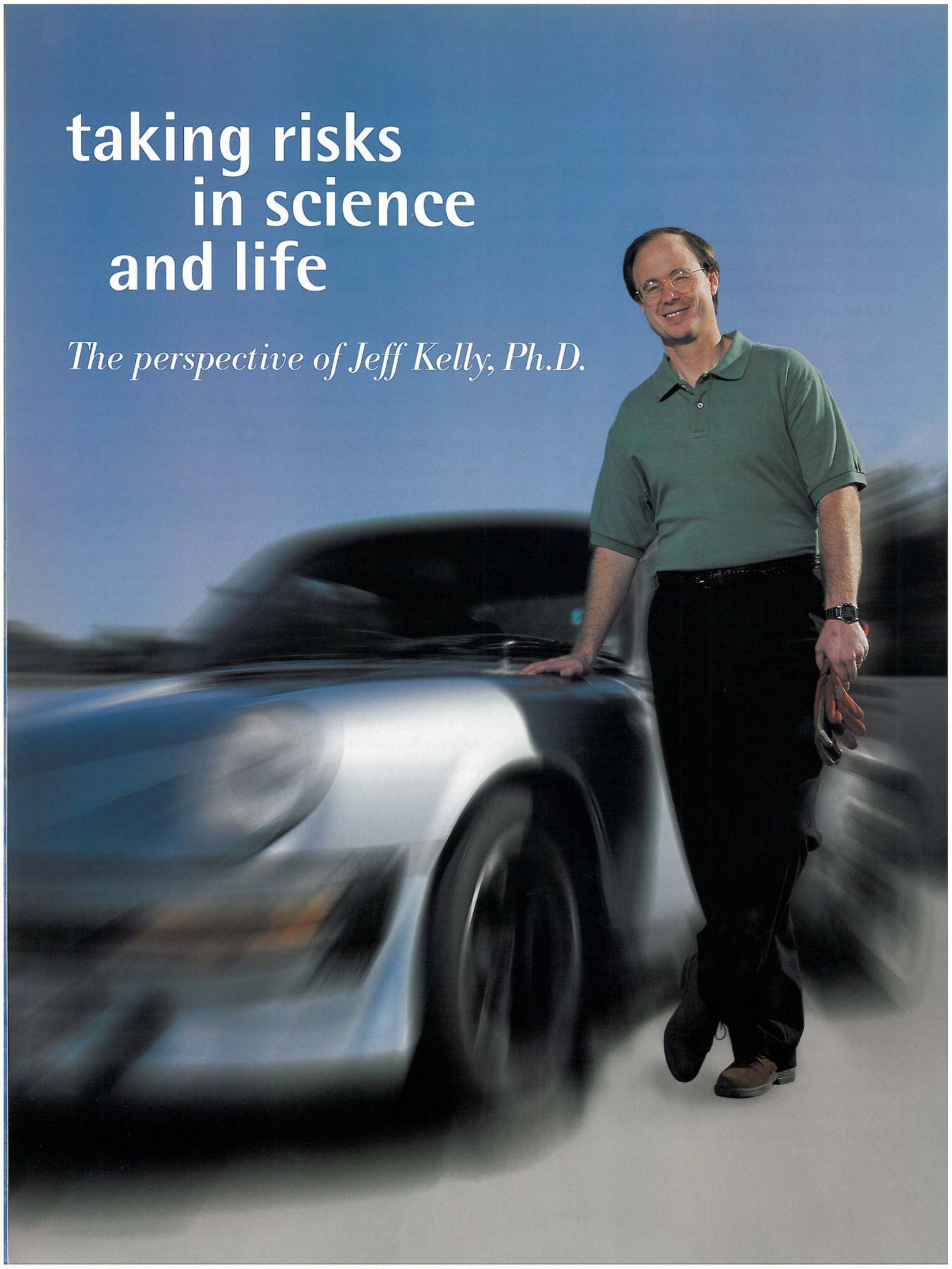
Predicting how proteins interact is critical to understanding the molecular basis of life. SurfDock is a program that represents the characteristics of the surfaces of proteins and predicts how they may interact. The image on the left shows two protein surfaces sliced open to show the complementarity of their shapes when they dock together.

This whimsical depiction is a hypothetical model of a designed triangular construction made up of virus building blocks. The polio viruses (in green) are used as hubs and tobacco mosaic viruses (in yellow) are used as spokes. In theory, such designs could be made to self-assemble with atomic accuracy into structures the size of integrated circuit components or larger.



taking risks in science and life

The perspective of Jeff Kelly, Ph.D.



Jeffery W. Kelly, Ph.D., Professor, Department of Chemistry, and The Skaggs Institute for Chemical Biology, arrived at The Scripps Research Institute a year ago with a big goal in mind.

He wanted to see if it was possible to prevent the formation of amyloid fibrils in patients with neurodegenerative diseases such as Alzheimer's and, just possibly, cure the disease itself. In decades past, these insoluble fibrils were neither well understood nor well tolerated. In fact, scientists who discovered them in their laboratories dismissed them as an obnoxious side effect of leaving proteins in solution a little too long. One biochemist called it "the gunk at the bottom of the test tube, the stuff everybody wanted to throw away."

As science learned more about diseases like Alzheimer's, they began to recognize similarities between the material in the test tubes and the way protein plaque formed in the brains of Alzheimer's patients. Although gunk formation has a certain exuberant quality to it, the protein aggregation process goes by the more scientifically accurate title of protein misfolding.

Starting out in basically the shape of a softball, something forces these proteins — composed of strings of amino acids — to change shape in abnormal ways in those patients with Alzheimer's disease and some dozen other similar diseases. Instead of completing the normal process to become separate mature proteins, these incompletely folded proteins — adolescent proteins, if you will — begin to cling to one another. This chemical clinging soon turns into a full embrace and the result is the formation of insoluble fibril aggregates, the test tube clogging material that scientists once threw away. But in human brain tissue, not test tubes.

Which is about where Jeff Kelly came in. Before coming to TSRI, Kelly was a professor of chemistry at Texas A&M (and before that at Rockefeller University in New York) and had been wondering about those amyloid deposits himself.

"It seemed unusual to me that people weren't considering amyloid diseases in the context of protein misfolding," he said, "since amyloid fibrils seemed to be composed of protein that is clearly in a different structure from the normal soluble and functional form."

INTEGRATION OF BIOLOGY AND CHEMISTRY

Which brings us to the interface of chemistry and biology and why Kelly came to TSRI in the first place.

"The experiments we're doing come directly from working at the interface of chemistry and biology," Kelly said. "At Scripps, we have the ability to produce small molecules that inhibit this abnormal protein folding. We're not developing drugs, but we are developing strategies to create new drugs."

While the average academic department remains narrowly focused on its subject area, at TSRI those sorts of boundaries don't exist.

It was the presence of that interface and the way the Institute views its role in the evolving world of research that brought Kelly to TSRI. A point of view, according to Kelly, that is different from most research institutions. While the average academic department remains narrowly focused on its subject area, at TSRI those sorts of boundaries don't exist. Here, Kelly pointed out, they put chemistry and biology on the same floor; a physical metaphor for what he sees as the Institute's more scientifically creative bent.

Kelly explains that they use chemical principles to solve biological problems while drawing heavily on the research tools of both. But where biologists tend to think in macro terms — whole species or at least whole

Facing page:
Jeffery W. Kelly, Ph.D., with his 1980 Porsche 911 SC.

animals — Kelly and his laboratory team tend to think in smaller, more molecular terms.

All of which is even more interesting when you consider the fact that Kelly barely knew chemistry or biology even existed until he was almost a graduate student himself.

SCIENTIFIC CREATIVITY

As an undergraduate in the SUNY system he planned on an engineering career until a summer with General Motors convinced him that engineering was not for him. But chemistry seemed to be a wide-open field: "It was less defined than engineering, more abstract. Besides, I really liked lab work. I still do."

But if you wanted to do lab work, Kelly quickly learned, you had to go to graduate school. He earned his Ph.D. from the University of North Carolina at Chapel Hill. After that, he thought about going to work in the pharmaceutical industry, but headed instead in the direction of academia.

"It really is a simple story," Kelly said, a phrase that he uses frequently, even when the story isn't as simple as it sounds. "I was a good research person. I liked going into the lab and discovering new things that excited me. And I liked academic research because I could pursue things that didn't have an immediate pay off."

This decision also taught him something about the nature of modern research and the kinds of scientific risks that organizations were willing to underwrite.

"One of the hard things about science these days," Kelly said, "is that you quite often need an extreme rationalization for everything you're doing or people won't consider it worth doing. If you can't explain why you're doing a project — usually a very specific why — you stand a good chance of not getting it funded. It's a dangerous way of thinking."

In academia you can still do basic research, he said, and then added a complex coda to that simple statement.

"Having said that," Kelly offered, "I don't think you can do it 100 percent of the time anymore. A well-funded lab has to appeal to someone who's intelligent about technological and scientific issues. But if only a few people in the world understand your science, you're going to have difficulty doing your research."

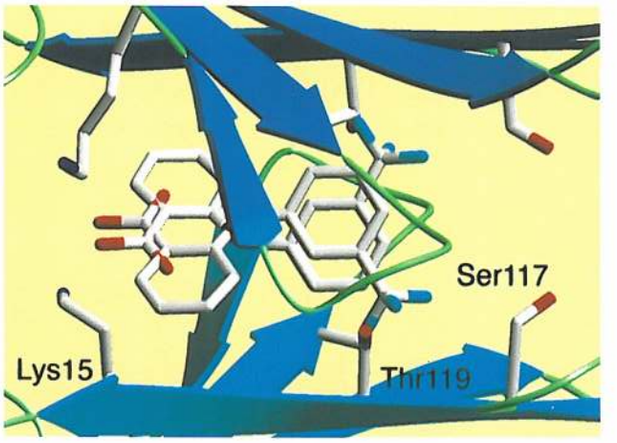
Kelly can explain his amyloid research quite clearly and with a scientist's carefully considered passion. Neurodegenerative diseases are characterized by the destruction of neurons. This is what happens in Alzheimer's disease. What is not so clear is whether amyloid plaque is the cause of neuron death or the result of it — that something in dying neurons triggers the abnormal protein folding process.

Kelly points out that in the few cases of Alzheimer's disease that scientists do understand — the familial form — it is a genetic mutation that makes the abnormal protein folding easier and faster. In 95 percent of Alzheimer's cases, however, there is no genetic mutation, so no one really knows what sets the disease process in motion.

A HYPOTHESIS FOR THE CAUSE OF ALZHEIMER'S

But like any good detective, Kelly has a good hunch. He thinks the protein did it.

"There are many, many people who believe this hypothesis, that the fibrils cause these diseases and there are lots of people working on it. The pharmaceutical industry has invested many millions in it as well."



Ribbon diagram representation of an X-ray structure of the amyloid forming protein transthyretin bound to a small molecule inhibitor that prevents amyloid fibril formation. This inhibitor, discovered by the Kelly laboratory, is now being evaluated in an animal model of amyloid disease.

None of which makes it so, Kelly would be the first to admit.

"We're testing this hypothesis. If it's correct, the small molecules we've developed to prevent fibril formation should stop the disease." As a backdrop to this theory, Kelly and his graduate students have shown that one of the small molecules blocks the formation of fibrils in vitro, confirming in Kelly's mind, at least, that this small molecule has the capacity to inhibit what happens inside the cell. He hopes to begin animal testing before the year is out.

"If the hypothesis proves to be promising in animal

models, then a tremendous amount of effort will be placed on finding small molecules that prevent fibrils from forming," Kelly said. "Millions will be spent on it. The challenge then will be to develop a unique agent for each form of the disease. But once you validate the target, you can go to town."

Then he reminds you just how new and risky this hypothesis really is: If you talked this way ten years ago, he says, people laughed at you.

TAKING RISKS

Which brings us around to the question of risk and Jeff Kelly's 1980 Porsche 911 SC.

It is a simple story. Back at Texas A&M he was looking to buy a car — a Honda, actually — when the banker he was borrowing money from loaned Kelly his Porsche for the weekend instead. He fell in love with the car.

"I knew a lot of mechanical things," Kelly said, "but I didn't know how to drive it. I owned it a year before I drove it at a Porsche Club event for the first time. After that I became the Club's instructor, not because I was a good driver but because of my organizational skills."

As he puts it, the Porsche Club Kelly served was one of the worst in the world, so bad that Porsche Clubs of America wanted to shut them down out of institutional embarrassment. Porsche sent a professional driver to observe the club's attempts at resuscitation and Kelly quickly snagged him as an instructor. Over the next three years, Kelly learned how to drive competitively and the club is now one of the best in the country.

"You start out doing driver education events on a road course where you're pretty limited to what you can do in terms of speed and passing. Then you get into vintage car racing where your car must have all its original equipment to compete. Basically, I ended up backdating my Porsche."

It wasn't long after this, and a few winning turns of his own, that Kelly began driving other people's cars, tearing through road courses at speeds that reached 160 miles per hour on the straightaways and averaged 85-90 mph on the rest.

The notion of risk did not seem to worry him, although he was certainly aware it existed. Kelly claims to never have seen anyone taken to the hospital in the ten years he's been racing and has banged up his car only once on a guardrail. "Remember, we're doing it for fun," he said. "I don't take reckless chances. If there's a 95 percent chance of passing another car, I'll do it. If there's a 20 percent chance, I won't."

Kelly said he takes far greater chances in the lab than he ever does on the track.

In Kelly's mind, you must never be afraid to do an experiment, regardless of the possible outcome.

"We do experiments that have a 1 percent chance of succeeding but that's the key to success in science," he said. "We had a visiting scientist who was so certain that an experiment would fail that he didn't even bother to do it. As it turned out, he was wrong in a highly significant way."

In Kelly's mind you must never be afraid to do an experiment, regardless of the possible outcome. He also realizes that fewer and fewer people, both in and out of science, share his idea of acceptable risk.

"Funding doesn't reward risk," he said. "Of course, if you're smart and good, the NIH won't argue with your success. TSRI has the resources to do this kind of research, high risk, high pay off experiments."

A FERTILE SCIENTIFIC ENVIRONMENT

The Scripps environment has allowed him to think big, to tackle groundbreaking experiments, and not just for the obvious reasons.

"You perform at the level of your competition," Kelly said. "It's like racing. Sometimes you get to the track and you discover that your lap time has gone down by two seconds because the other drivers are so good. I swear that the ability of my graduate students has gone up by an order of magnitude because of the competition here. You don't have to look too far to find somebody at TSRI that you envy, me included. It focuses you to do better work." ■

John Moores contributes to The Scripps Research Institute to create new Institute for Childhood and Neglected Diseases

The Scripps Research Institute recently announced the establishment of a new Institute for Childhood and Neglected Diseases on its campus in La Jolla, California. Its purpose is to apply the new molecular understanding of biology to address, reduce and treat recalcitrant illnesses in two major categories — childhood diseases, and neglected diseases that affect populations primarily in developing countries. A unique collection of 26 exceptional automobiles has been contributed as a lead gift for this new effort by businessman, San Diego Padres owner, and philanthropist John Moores and his wife, Becky.

Businessman, San Diego Padres owner and philanthropist, John Moores

The new initiative will build on the strength that TSRI has achieved at the nexus of biology and chemistry through the establishment of The Skaggs Institute for Chemical Biology, according to TSRI President and CEO, Richard A. Lerner, M.D.

He continued, "The extraordinary generosity of the Moores family will make it possible for The Scripps Research Institute to take the deluge of knowledge amassed by the Human Genome Project and uncover a deeper understanding of the mechanisms underlying human disease than has ever been possible before. Scientists will undertake a systematic effort to study not only the genes themselves but the interactions between them. Over the long term, we expect that this approach will lead to medical achievements that are unimaginable with current technology. Further, our ability to integrate the activities of this new entity with The Skaggs Institute should enhance our efforts to alleviate human suffering through a multiplicity of scientific discoveries."

USING KNOWLEDGE FROM THE HUMAN GENOME PROJECT

Scientists believe that biology and medicine in the coming century will look very different from the way they do now. The human genome, the totality of genetic information inside the human body, is expected to be deciphered in the next three years. For the last several years, scientists have been isolating individual genes, lately at an accelerating pace. The identity of these genes has yielded glimpses inside the machinery of the body. But it has been difficult to look at genes in the larger context of how they interact with each other and with their surroundings in the cell and the body. Further, the regulatory mechanisms that have been discovered frequently turn out to be small parts of the larger, more complex cascades.

Scientists at TSRI are preparing to apply the burgeoning knowledge of genes and their interactions to specific childhood and early-onset diseases. The creation of the Institute for Childhood and Neglected Diseases will bring together scientists from throughout the world to investigate such diseases as childhood cancers and leukemias, cystic fibrosis, Duchenne's muscular dystrophy, and autism. In addition, TSRI and Children's Hospital and Health Center, San Diego, have begun initial discussions on ways in which the two organizations can collaborate to improve the health of children locally and internationally.

Blair Sadler, President and CEO of Children's Hospital, commented, "Each year Children's Hospital and its affiliated physicians provide services to more than 350,000 children. We are excited by the opportunity to combine our depth of clinical experience in pediatric medicine with the extraordinary scope and quality of science offered by the Institute. We believe that this collaboration will reinforce importantly the missions of both institutions."

NEW TREATMENTS FOR PARASITIC DISEASE

The majority of the world's population — those who live in developing countries — has not yet reaped the benefits of the genetic revolution. But some effective initiatives have been launched, and the new Institute for Childhood and Neglected Diseases will use the latest advances in biology in an effort to find novel treatments for widespread and often devastating parasitic diseases.

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. These recent efforts promise to bring advances in fighting diseases still rampant in the developing world.

The World Health Organization has named a handful of

"target diseases" in its tropical disease research program. They include the parasitic diseases malaria, schistosomiasis, trypanosomiasis, and leishmaniasis that collectively endanger some 500 million people and kill nearly two million people each year. The

"Over the long term, we expect that this approach will lead to medical achievements that are unimaginable with current technology."

Institute for Childhood and Neglected Diseases plans to build on the work of a number of TSRI scientists in such areas as schistosomiasis and malaria and will focus its efforts on understanding the mechanisms of action in major parasitic diseases.

The new Institute will include state-of-the-art research laboratories in a facility to be constructed on TSRI's campus on the east side of North Torrey Pines Road. The project architects are Todd Williams and Billie Tsien, who designed The Neurosciences Institute.

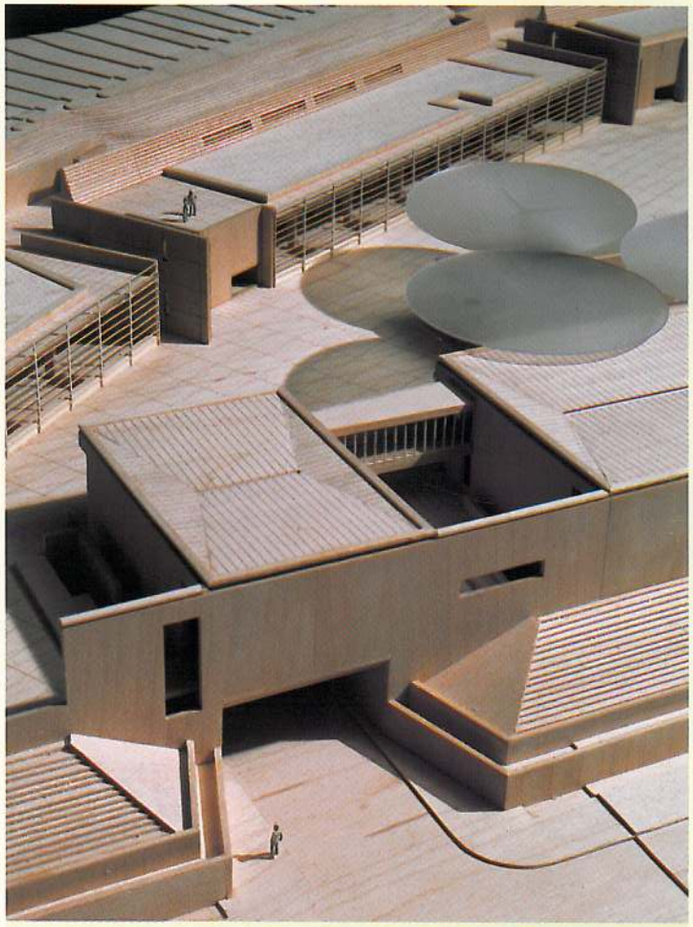
CONTRIBUTION OF AUTOMOTIVE ENTHUSIASTS

The initial fundraising effort for the Institute for Childhood and Neglected Diseases has been undertaken by a generous group of automotive enthusiasts, including John Moores, and spearheaded by the owners of the Symbolic Motor Car Company, Bernard and Marc Chase, and Bernard Glieberman.

TSRI has an ongoing relationship with the community of car collectors, having been the beneficiary of the Torrey Pines Concours d'Elegance for the past two years. These collectors have offered to donate a number of rare and exotic automobiles, the proceeds of which will be contributed to the Institute for Childhood and Neglected Diseases. Four such cars — including one of John Moores' NART Spyders — were auctioned at Christie's Auction of Exceptional Automobiles at the Concours d'Elegance in Pebble Beach, August 16. In addition, several other cars from Mr. Moores' collection were auctioned that weekend at the Monterey Sportscar Auction presented by RM Classic Cars and at an auction sponsored by Brooks USA for a total of $2.6 million. As a gesture of appreciation, TSRI will make available a portion of the new facility in which collectable items of automobilia will be displayed by donors.

In addition, 15 automobiles were auctioned by Christie's on October 17, 1998, at The Scripps Research Institute, preceding the Torrey Pines Concours d'Elegance on October 18. Proceeds from the sale of all vehicles benefit the Institute for Childhood and Neglected Diseases.

According to Bill Evans, President of the Evans Hotel Group and Chairman of the Torrey Pines Concours d'Elegance, "We are delighted that the Concours will benefit the new Institute for Childhood and Neglected Diseases at TSRI. The generosity of the Moores family is greatly appreciated and we are hopeful that others will follow their example." ■



A model of the Institute for Childhood and Neglected Diseases

TSRI Researchers Win Prestigious Scientific Awards

TSRI scientists are the recipients of scientific awards for a variety of significant research achievements.

K. Barry Sharpless, Ph.D., *W.M. Keck Professor of Chemistry in the Department of Chemistry and The Skaggs Institute for Chemical Biology,* was honored for his accomplishments by the Technion-Israel Institute of Technology. He received the Harvey Prize for his contributions to chemistry at an awards ceremony in Israel. Sharpless is best known for using metal catalysts to create useful new methods for synthesizing organic molecules and asymmetric compounds in particular.

Chi-Huey Wong, Ph.D., *Ernest W. Hahn Professor, Department of Chemistry and The Skaggs Institute for Chemical Biology,* received the ACS Claude S. Hudson Award in Carbohydrate Chemistry, sponsored by National Starch & Chemical Co. The award recognizes outstanding contributions to carbohydrate chemistry in education, research or application. Wong specializes in the production and use of natural or modified enzymes for organic molecules. This emphasis has important implications for efforts related to the creation of rationally designed drugs.

K.C. Nicolaou, Ph.D., *Chairman and Skaggs Professor of Chemical Biology, Department of Chemistry, and The Skaggs Institute for Chemical Biology,* received the Gustavus John Esselen Award for Chemistry in the Public Interest for outstanding achievement in scientific work which contributes to the public well being and "in recognition for his revolutionary approach to natural science." Sponsored annually by the Northeastern Section of the American Chemical Society, the award was presented in a ceremony at Harvard University.

Mark Yeager, M.D., Ph.D., *Associate Professor in the Departments of Cell Biology, Molecular Biology and Vascular Biology, and a cardiologist and Director of Cardiovascular Research at Scripps Clinic,* is the recipient of a Clinical Scientist Award in Translational Research from the Burroughs Wellcome Fund. He is one of ten U.S. and Canadian researchers who collectively have been awarded $7.5 million to "bridge the gap between the laboratory bench and patient care."

Dale Boger, Ph.D., *Richard and Alice Cramer Professor, Department of Chemistry and The Skaggs Institute for Chemical Biology,* is the recipient of the American Chemical Society Award for Creative Work in Organic Chemistry, sponsored by Aldrich Chemical Co., Inc. His research interests include the total synthesis of natural products, the development of new synthetic methodology, bioorganic and medicinal chemistry, and the chemistry of antitumor antibiotics.

Kim D. Janda, Ph.D., and **M. Reza Ghadiri, Ph.D.,** both *Professors of Chemistry, Department of Chemistry and The Skaggs Institute for Chemical Biology,* have been awarded the American Chemical Society's Arthur C. Cope Scholar Awards, recognizing outstanding achievements in the field of organic chemistry. Janda's research interests include studies on catalytic antibodies and enzymes, reactive immunization, immunopharmacotherapy for the treatment of cocaine abuse, antibody-antigen interactions, and reversible and irreversible inhibitors of the HIV protease. Ghadiri's research efforts involve developing novel methods for the rational design and construction of biomaterials-based membrane channels, artificial proteins, molecular receptors, and enzymes. ■

Editor:
Robin B. Goldsmith

Writers:
Steven Dickman
Eric Sauter

Illustration:
Steve M. Lustig
BioDesign Communications Inc.

Design:
Craig Fuller
Sandra Sharp
Greenhaus

Production:
Negar Ashraf
Damian Moos

Photography:
Jeff Tippett

Printing:
Continental Graphics

THE SCRIPPS RESEARCH INSTITUTE

Office of Communications
10550 North Torrey Pines Road
La Jolla, California 92037

NON-PROFIT
U.S. POSTAGE
PAID
PERMIT 751
SAN DIEGO CA