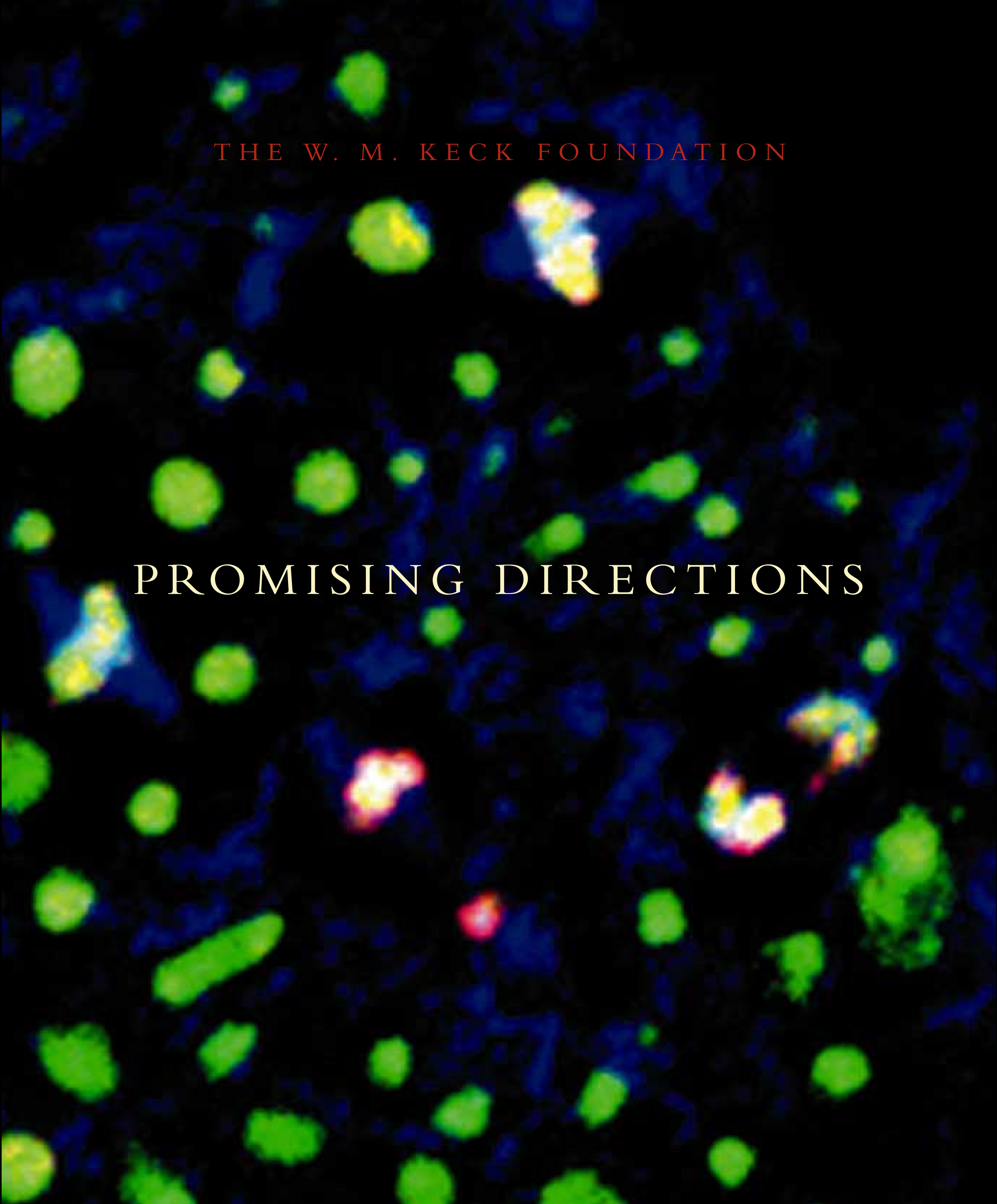
THE W. M. KECK FOUNDATION

PROMISING DIRECTIONS



ABOUT THE FRONT COVER:

A field of mitotically dividing cells in the fruit fly embryo. The DNA appears green, the mitotic spindle that separates the chromosomes blue, and the condensed, segregating chromosomes appear yellow. *Whitehead Institute for Biomedical Research*

ABOUT THE BACK COVER:

The planet Neptune as observed on May 24, 1999 using the new adaptive optics at the W. M. Keck Observatory in Hawaii. Images were obtained in broad band J and H (blue and red, respectively) and in the methane absorption band within the J band (green). These three images were combined to create the "true" color image shown at the top. *W. M. Keck Observatory*

PROMISING DIRECTIONS

THE W. M. KECK FOUNDATION

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REFLECTIONS FROM THE CHAIRMAN

While the cynics may say it's just another date on the calendar, the turn of a millennium is as appropriate a time as any to lift our eyes from our day-to-day work and cast them toward the horizon. The W. M. Keck Foundation did just that on two very special days last May when we convened a pair of roundtable discussions to ponder the future of science.

Moderated by the Foundation's Senior Scientific Advisor, Dr. Thomas Everhart, the W. M. Keck Foundation was honored to host seventeen of the finest and most accomplished scientists in the nation for a pair of conversations held on successive weekends in New York and Los Angeles.

For the Foundation, the purpose of these meetings was simple: to gain the front-line perspective of leading investigators on the most promising directions in science today, and on the impediments to realizing the vast potential before us. For our participants, we hope it was a respite from the pressing demands of their work, a chance to exchange important ideas with their peers, and an opportunity to inform the future grant-making priorities of the W. M. Keck Foundation, and hopefully other foundations as well.

The participants in our roundtables were drawn from across a wide range of disciplines in the physical and life sciences, engineering and medical research, and a variety of backgrounds, from working lab scientists to heads of private institutions and government agencies. What they share is a record of outstanding scientific achievement and leadership in their respective fields of inquiry.

To facilitate the discussions, we asked the participants to make a brief presentation addressing their perspectives on the greatest opportunities and challenges facing science as we enter the 21st century. These presentations were followed by an active and free-flowing discussion that, like any scientific effort worth its salt, brought clarity to some questions and added new facets to others.

In the end, the Foundation was left with a wealth of information in the form of sixteen hours of video, which our staff has painstakingly reviewed to produce this report. Our roundtable participants' comments centered on two broad categories: one addressing research priorities and possibilities; the other examining the processes and policies needed to produce an environment that encourages creative science. We have attempted to distill these remarkable conversations to their essence and we are pleased to share them with you in the following pages.

Where we felt we and others would benefit from closer examination of a particular topic, we asked one of our participants to contribute a brief essay. These too are reprinted here. These essays represent a rare collection of our leading scientists' insights into issues that in some way affect us all.

The result, we sincerely hope, is a book that shares the best thinking on some of the most important questions of our day. And if we've done that, then we've achieved the first part of our goal. The second will be to continue the legacy of the W. M. Keck Foundation by building on what we have learned to continue making bold grants that make scientific breakthroughs possible for the benefit of humanity.

Finally, on behalf of the Board of Directors and staff of the W. M. Keck Foundation – and everyone who finds this book of value – I want to extend my gratitude and appreciation to each of our roundtable participants for their time and dedication.

ROBERT A. DAY

CHAIRMAN, PRESIDENT AND CHIEF EXECUTIVE OFFICER

W. M. KECK FOUNDATION

SCIENCE AT THE BEGINNING OF THE TWENTY-FIRST CENTURY

A SUMMARY OF THE ROUNDTABLE DISCUSSIONS COMPILED
BY THE W. M. KECK FOUNDATION STAFF

When the Foundation decided to convene the roundtable discussions on the future of science, we were unsure what to expect as a result. We knew only that with two discussions taking place on both sides of the continent involving seventeen of the world's brightest scientific minds, the conversation would be intriguing. We also knew that the situation promised a serious potential for information overload.

While we were flooded with information, discernible patterns emerged to help make sense of it. The participants came to a surprisingly strong consensus on a number of key themes that they felt would define the direction of science in the next ten years. The most fundamental of these was a sense that the predictive power of science is poised for an unprecedented leap forward.

The springboard for this great jump will be the rapid advance of technology, especially ever higher-throughput data collection instruments and networks coupled with sophisticated computer modeling tools. Many of our guests also signaled a need for a renewed emphasis on the development of theories to guide the processing and understanding of this wealth of data. Together, these new tools and theories could lead to a deeper understanding of nature, and improve our ability to devise solutions to nature's mysteries that will provide lasting benefits for humanity.

Underlying these broad themes were several specific areas that our roundtable participants believe represent the greatest opportunities to advance our knowledge and understanding of nature in the next decade. These include:

- Miniaturization: miniaturizing sensors, instruments, computers, and other systems using nanometer-scale components
- High-throughput Data Acquisition: collecting large data banks of information
- The Data Problem: extracting desired information from these databanks
- Post-Genomic Biology: learning the function of genes and the proteins they encode
- Complexity: understanding the intertwined nature of life at the micro and macro scales.

In the following pages we have endeavored to capture the essence of two days of remarkable conversations about the challenges we face, and the opportunities we may realize as science moves forward in these promising new directions.

MINIATURIZATION

"One nanometer is a magical point on the scale, because within two orders of magnitude on either side, you have the smallest manmade devices, and you have the molecules of living systems." With these words, Dr. Eugene Wong summed up the excitement about the potential for the miniaturization of scientific instrumentation to open up new worlds of discovery. Visions for applications ranged from a "lab in a box" to a "computer on a chip." To realize these visions, however, the roundtable participants stressed the need for a new paradigm governing both the architecture and techniques involved in miniaturization.

Current fabrication techniques have served us well, commented Dr. Evelyn Hu, taking us from "the transistor in 1948 to the ultra-large scale integration of chips that we see now." Although the first transistors were "three dimensional and clunky," she continued, "as people made the leap to fabricating many of them at a time, the paradigm became a two-dimensional process, printing electronic functionality layer by layer with the appropriate alignment, somewhat like a multi-color page." Dr. Hu then drew a comparison from history: "Just as Gutenberg's invention of the printing press revolutionized the transformation and dissemination of information in his time, this parallel-processing paradigm revolutionized the integrated circuit. But is this the relevant paradigm we should be adopting today?"

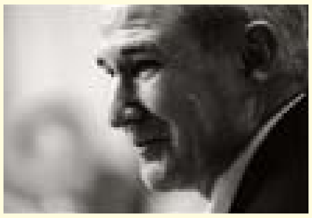
What new paradigms are being investigated that will create multi-functional nanometer-scale devices? One widespread effort is geared at learning how to reliably integrate the current silicon-based electronic circuitry technology with optical and mechanical technologies in what are essentially two-dimensional units. Communication across units in these micro-electro-mechanical systems (MEMS) will be reliant upon the successful addition of a new dimension – movement – both within a unit and between different levels of such structures. Some success has been reported already in this area, and Dr. Noel MacDonald predicted that "photonics chips are going to be in personal computers within five years. We are then going to have all this beautiful technology we can apply to biology: photonics, electronics, and the electro-mechanical chips."

Beyond these critical first steps, however, are the challenges of incorporating organic and even biological molecules with silicon- and non-silicon-based surfaces. Perhaps the most obvious problem is that the same molecules that are essential to the function of biological molecules, such as salts, destroy the function of semi-conductor materials. This makes the reliable interaction of chip surfaces with organic or biological molecules difficult, but not impossible. Dr. MacDonald outlined some of the possibilities such biochips and biosensors would facilitate, including networks of millions of chips providing active or passive monitoring of an environment for detection of toxins, drug delivery monitored through implantable sensing chips, and three-dimensional molecular patterning of new materials by computers fed by networks of bio- and MEMS-chips.

Among the myriad potential uses of biological molecules with engineered properties is the application of the

DR. THOMAS EVERHART

DR. EUGENE WONG



DR. NOEL MACDONALD

"ONE NANOMETER IS A MAGICAL POINT ON THE SCALE, BECAUSE WITHIN TWO ORDERS OF MAGNITUDE ON EITHER SIDE, YOU HAVE THE SMALLEST MANMADE DEVICES, AND YOU HAVE THE MOLECULES OF LIVING SYSTEMS."

DR. EUGENE WONG

DR. EVELYN HU

DR. DAVID SCHWARTZ

"POST-GENOMIC IS NOT A REAL PHRASE, BUT A METAPHOR FOR AN ERA IN WHICH WE ARE GOING TO BE FLOODED WITH INFORMATION."

DR. DAVID SCHWARTZ

technology to create molecular scaffolding or molds that can then direct the construction of nanodevices. At the University of Chicago, for example, scientists are genetically manipulating proteins to form fine interwoven strings that may serve as templates for new materials. Such structures may interface with current chip technology and provide the basis for powerful optical signal processing tools, among other applications. An advantage of using biological systems to create miniaturized structures is that they are often able to self-assemble. As Dr. Hu stated, "Nature has dealt with the problem of self assembly in a far better and more reliable way than we practitioners working with electronic materials have been able to do."

So where does all of this lead? What other practical applications of nanoscale instruments and detectors might we look forward to using? According to our participants, advances in miniaturization will lead to higher device density, which in turn will lead to the development of scientific instruments of greater complexity and power. This might be the "lab in a box" envisioned by Dr. David Schwartz, which combines a DNA sequencer, tissue culture facility, and confocal microscope all on one desktop, with each instrument capable of detecting molecule-sized samples. The instruments would feed data into a computer which itself could be nothing more than a PC contained on a single chip.

Finally, there is the tantalizing possibility that by constructing nanoscale devices, scientists will discover new physics. As Dr. Hu noted so eloquently, "Scaling brings surprises, and those surprises are of fundamental scientific interest, not only for the application they may be ultimately designed for, but because they inform and delight and give us more information about basic physical phenomena."

"THE DATA PROBLEM"
HIGH-THROUGHPUT DATA ACQUISITION

As evidenced by the potential nanotechnology revolution, the development of new technologies is a powerful driving force behind advancement for all types of science. In the area of imaging, for example, technologies such as scanning tunneling, atomic force, and multi-photon microscopes, coupled with new sample preparation and tagging techniques, allow scientists to observe single atoms in real time. On the other end of the size scale, the Hubble Space Telescope and new state-of-the-art adaptive optics on the Keck Telescopes are allowing astronomers to peer into the very origins of time and space.

Some of the most dramatic advances in science today are being made in the development of new data acquisition technologies, such as high-throughput DNA sequencing that makes it possible to sequence entire genomes in months instead of decades. Despite the oceans of data being generated by this and other technologies, however, our roundtable participants repeatedly stressed the challenge that lies in the development of still greater high-throughput data acquisition capabilities, coupled with the need for new tools to analyze that data to reveal new insights into the way nature functions.

Possibilities range from the "lab in a box" discussed earlier, to creating networks of existing experimental stations or observatories to share data, identify problems, and explore

DR. CLAIRE MAX

DR. DINSHAW PATEL

solutions. "Networking physical facilities, whether it's in earthquake engineering or in microelectronics, is a very attractive option," offered Dr. Wong. "Networking allows one to unify the databases, and to develop much larger heterogeneous models."

By way of example, Dr. Claire Max explained how a network of three modest-sized ground-based telescopes in different parts of the world would provide an inexpensive way to catalogue solar systems throughout our galaxy. The idea is quite feasible, and the potential payoffs enormous: "If every star that we looked at had planets, you would expect to discover roughly forty Jupiters and two Earths each year." These data, combined with other sky survey data, such as the enormous Sloan Sky Survey undertaking, could very well result in new understandings of the components of our universe, and new models on how it was formed and has matured.

All of these advances, and many yet to come to fruition, are creating an unprecedented increase in the quality and quantity of data collected. New methodologies will only increase this load. Our roundtable participants predicted a growing crisis: How can this data be "mined" for useful information? Conversely, how can the data be synthesized to make a sum greater than its parts? Theoreticians need tools to analyze seemingly disparate data to produce a theory that synthesizes observations into clarifying models.

DATA ARCHIVING

Brandishing a magazine cover which read, "Are Astronomers Drowning in Data?," Dr. Max explained the "data problem" in astronomy: "There are several all-sky surveys going on right now. These will be crucial for understanding the statistical structure of the universe, but the data volumes are absolutely huge. The typical survey today is a few terabytes per year, and there's every sign that it will be a factor of ten higher than that in the next generation. There is a severe need for automated image processing, data mining, and new visualization tools. How do you even find out if there's something interesting in your data with these large amounts of information coming in? This requires a real collaboration between astronomers and computer scientists."

The same is true for studies at the atomic level. As biophysicist Dinshaw Patel noted, "Like our crystallography colleagues, we would like to be able to solve structures and understand their function in a high-throughput way, both for proteins and for RNA." He explained that the ability to do so would greatly aid computational biologists' understanding of protein folding states, how chaperones are involved in protein folding, functions of membrane proteins, and other "holy grail" questions.

Dr. Will Happer pointed out another seemingly prosaic, but also critical problem: data storage. "I would venture to say that when we look at databases twenty years from now it may be easier to find the Chinese data on the Crab Nebula explosion in 1054 AD than to see some of the databases that we put together now because we can't figure out how to read the storage media." Sounding a warning to all scientists, he continued, "We need to be able to archive information so we can be sure that our successors can retrieve it." Why? Future generations of scientists will need access to raw data, not just results, as their theories and models obtain greater levels of sophistication.

DATA SYNTHESIS: THEORY, SIMULATIONS, AND MODELING

In fact, several participants noted that science in general needs more theories, especially at the systems level, to start dealing with the observational data that is approaching us at a furious pace. Just dealing with the huge amounts of data currently being collected is a challenge. Accurate models and simulations of physical and biological events in which systems can be tested for accuracy are essential to the advancement of our understanding of nature. This will then drive the need to test theories, relying on a combination of experimentation and modeling, so that each informs the other in a continuous feedback system. Models need to inform our data acquisition as much as the data contributes to modeling.

"Theory is central to searching for the ultimate laws, such as quantum gravity, motivating new experiments such as LIGO, and milking the essence from the simulations and observations that we do, and connecting disparate phenomena with each other. I've been involved in all of these and I think theory is vastly underestimated in its power, and it is under-practiced in its roles in fields such as those I've been involved in," explained astrophysicist Kip Thorne.

Theory is not only lagging far behind in the physical sciences; it is almost entirely absent from the biological sciences, according to our discussants. Theory is necessary to inform modeling and simulation experiments, which, as we have seen, are necessary to help interpret the vast amounts of data being accumulated. At the crux of all of this is computation. According to Dr. Marvin Cassman, "The interesting thing about bioinformatics is the intellectual contribution that computer science can make for understanding biological systems."

Dr. Gerald Edelman agreed. "One of the most important things we can do in neuroscience is to model extraordinarily complex neurological events." These goals may be easier to realize in theory than in practice, however. Dr. Michael Bishop raised an important issue when he questioned whether many areas of the biological sciences are ready to benefit from intense computational modeling. He suggested that a symposium to study this critical issue would be invaluable and timely.

On the flip side, Dr. Ivan Sutherland noted that computer science doesn't yet have all the techniques and tools that physical and biological scientists require to handle their data and generate models, either. "The biggest problem facing the com-

"I WOULD VENTURE TO SAY THAT WHEN WE LOOK AT DATABASES TWENTY YEARS FROM NOW IT MAY BE EASIER TO FIND THE CHINESE DATA ON THE CRAB NEBULA EXPLOSION IN 1054 AD THAN TO SEE SOME OF THE DATABASES THAT WE PUT TOGETHER NOW."

DR. WILLIAM HAPPER

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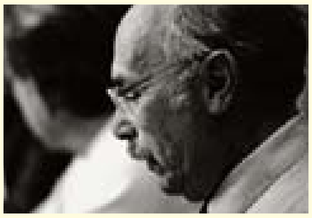
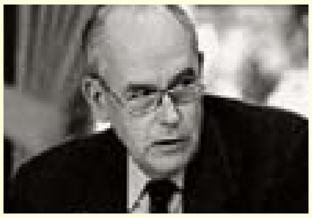
DR. KIP THORNE



DR. MARVIN CASSMAN



DR. IVAN SUTHERLAND

DR. SHIRLEY TILGHMAN

puting research field is parallelism," he explained. "Computers grew up with sequential programming, and every programming language that is used today describes operations in sequence. I think there will be a paradigm shift forced on the programming community by parallel machines as concurrency becomes the basis of the language, and not an add-on. Such new forms of expression are among the many tools that are needed" to allow computational science to fulfill the promise envisioned by many of our participants.

Another roadblock slowing progress in this area is that of forging truly useful interdisciplinary collaborations. Dr. Cassman explained that, in the instance of a collaboration between a mathematician and a biologist, "the problem is the mathematician has to understand biology. One reason why biologists are so negative about modeling and mathematical theories is that the attempts to do this in the past have given the biologists answers they didn't want. The modeling required too much simplification" to be useful. Training individuals who are conversant in the ideas and languages of other fields is key to removing this roadblock.

Participants repeatedly endorsed the need for new paradigms for collaborations. Dr. Max noted that "foundations such as Keck should think about how to incentivize some of these interactions." This and other issues pertaining to the human aspects of doing science are discussed in the second half of this report.

LEAPING AHEAD:
DATA MINING AND THEORY INFORM EACH OTHER

Many questions will not yield their answers through a simple cataloguing of data. Dr. Shirley Tilghman predicted that soon we would be adapting "to a world in which we will no longer be acquiring data, but beginning to exploit data...to ask new and different kinds of questions about living systems." At the heart of what the panelists discussed is that scientists now have the potential not only to answer existing conundrums about life on this (or other) planets, but also to conceive and investigate questions as yet unthought of.

Some participants came ready to speculate on new approaches to the study of science that might help make this future a reality. Dr. Schwartz, at the New York roundtable, envisioned a tightly-honed feedback model (incorporating the "lab in a box") that attempts to emulate nature by rapidly gathering data and using that data to inform a continually evolving model. He explained the first steps: "You set up a series of experimental matrices to cover the variables you have decided to test. You can model chemical systems, biochemical systems, or a whole organism; and your model can be as multi-dimensional as the technology allows. Coupled to this theoretical model is a detection system that works in concert with your experimental assays." Then came the really intriguing concept: "The information from the detection system comes back into the databases, and the model is automatically refined. You can then put together massive experiments and join them with modeling analysis systems fed by other databases. Depending on the kind of technology, the size of the arrays, and so on, your model and the actual world start getting tighter and tighter, if you are lucky."

In a parallel discussion at the roundtable held in Los Angeles, chemist Peter Schultz came at the opportunity from a different angle: "Although we've made huge numbers of molecules, we've made barely a small fraction of what's possible with all the elements in the periodic table." He explained the opportunities inherent in high-throughput combinatorial chemistry and screening assays by calling the unmade and untested chemicals "unexplored territory." Dr. Schultz continued: "They are unexplored for interesting properties that are of interest to the chemist and to the physical and materials science communities who are looking for room temperature superconductors, new thermo-electrics, magnetic materials, optical materials for optical computing, information storage, new catalysts that are environmentally benign, ultra hard materials, batteries, and interfacial materials."

What is the roadblock? The consensus among our participants was that we lack the predictive tool set to exploit the chemistry. Dr. Schultz asked whether or not biological strategies and principles can be used to help make interesting physical entities. "What nature does is make molecules, billions at a time, then selects and refines. So instead of designing one experiment and analyzing it, one can design hundreds of thousands of experiments, execute them, and analyze them in parallel." Recent experiments in the Schultz lab have used this method to make novel combinations of materials that show unexpected and promising new optical properties.

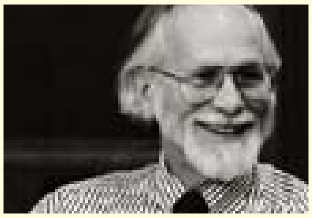
Scientists are anticipating a future where they can use evolution-like principles and massively parallel operations to discover and refine molecules with specific physical, material, biological, and chemical properties. As Dr. Schwartz explained, "It's clear that we've gotten very good at generating a lot of biological data, and we have to get better at dealing with it. Some people use this like a weapon and say, 'we've gotten fast enough, we shouldn't be going forward.' Wrong. We've got to go faster. We need to start making smart experimental systems."

POST-GENOMIC BIOLOGY

Biology is the field where this embarrassment of riches in terms of data will have the most profound consequences. Our ability to image living cells *in situ* will continue to revolutionize our understanding of the fundamental interactions between the genes, proteins, and cellular components that govern life. Additionally, advances in epidemiology, which collects and interprets health and environmental data at the level of entire populations, will allow researchers to start to unravel the complex micro- and macro-networks that determine the physiology, personality, and health of individuals. Ultimately, this will lead to powerful methodologies for predicting, preventing, and treating human diseases.

Cancer research is one field in which current methodologies are being pushed to the limit: "What we're hoping to work our way toward," said Dr. Bishop, "is a point where every individual tumor will be subjected to genetic profiling, and from that genetic profiling will come the ability to possibly infer cause, and certainly predict course and therapeutic response. In due course, this information will be used to create individualized therapies." Obviously, such individualized treatment would greatly improve the clinical outcome of cancer therapies, and is a highly prized goal of cancer researchers.

DR. PETER SCHULTZ



DR. MICHAEL BISHOP

One source of information that will aid such studies, according to Dr. Herb Pardes, are the often-reviled HMOs. Their large databases contain information on diagnosis, symptomology, and outcome that is invaluable. Dr. Schwartz cited the potential for high-throughput data acquisition to aid in these studies: "We'd like to cover entire genomes, and we'd like to have expression profiles covering a large number of tissue types under a large assortment of stresses, and we'd also like to combine this in metabolic profiling. The list goes on and on." When treatment plans nationwide report patient data in compatible formats, the ability of researchers to cull important information from these databases will be greatly enhanced.

Our participants were in almost universal agreement that the study of living organisms is becoming an interdisciplinary venture. Biologists, engineers, chemists, physicists, and computer scientists together are devising new methodologies and new conceptual approaches to tackling the tough questions, such as how ion channels work, or what networks of genes contribute to complex diseases like cancer or cardiovascular disease. This multi-disciplinary approach was championed throughout both roundtables. Dr. Lee Hartwell remarked, as one example, that the opportunities for collaborations between geneticists and combinatorial chemists are enormous and exciting. "Ideas about evolution and selection are certainly going to revolutionize drug discovery. This process is already well underway."

Another critical area for collaborations identified by the discussants is the development of robust computational tools for understanding living systems. As was noted earlier in this essay, the scientists agreed that there is a rarely bridged chasm between mathematical and computational models on the one hand and the sophistication of biological reality on the other. According to Dr. Cassman, "the interesting thing about bioinformatics, or at least computer science, is the intellectual contribution that it can make for understanding systems. There's a lot of interest, but at the intersection of computer science, mathematics, and biology, all you find are good intentions."

Dr. Wong agreed. "I think it would take a very good mathematician to ask a set of questions that would never occur to a biologist, and the answers might stun some biologists. As long as the questions are being asked by biologists, I don't think you're going to get the great leaps" forward necessary to truly advance our knowledge of complex systems, he said. This comment resonated strongly long after the roundtables were over. What questions should we ask? What projects will bring computer scientists, physicists and biologists, among others, together as equal collaborators, advancing each field as well as our specific knowledge? The future of biology relies heavily on new and insightful answers to these questions.

COMPLEXITY

Science is creating a new way of viewing nature. We are becoming increasingly aware that while relatively simple rules may govern cell reproduction, or the movements of stars and planets, a much more complex network intertwines everything in the universe. Pulling on one thread affects the entire garment in a

"WE HAVE GENES WITHIN US THAT WE RETAIN FROM AN INNOVATION TWO BILLION YEARS AGO."

DR. EDWARD STOLPER

variety of ways. The panelists were united by their awe of nature's complexity. This feeling was perhaps best given voice by Dr. Edelman. "I think one of the most challenging problems of modern biology is the problem of complexity. If someone asked me to close my eyes and imagine a cell, never mind a nerve cell, I don't think I could do it. The complexity of this system is dazzling, and certainly not one an engineer would put together at any reasonable economic expense," he observed.

The study of complexity will necessarily combine theoretical investigations with detailed individual studies of the mechanisms of change. The long-term goal is to understand which features of a phenomenon, whether they are biological, chemical, physical, or behavioral, are consequences of the internal organization of an object or organism, and which features are consequences of the history of the environment and selection imposed on that object. What phenomena are accessible to study from the viewpoint of complexity? The list is likely endless: a single protein molecule, a cell, a human, a culture, a planet, or a galaxy, just to name a few.

How do we begin to understand this complexity in a sophisticated way? As we learned at the roundtables, there are vast amounts of data to be sorted, indexed, catalogued, analyzed and synthesized. There are new conceptual approaches to be developed to make sense of the new experimental observations, to generalize from the specific. These theories will in turn inform and refine the next generation of experiments. Development of new instruments and combinations of instruments will be essential to realize the promise of these methodologies. Similarly, computers will continue to be essential, but will not achieve their potential until software design is radically different from today's sequential modes, and specialized, single task computers have been developed to support these endeavors.

Two participants summarized, from very different perspectives, the rewards awaiting scientists who take on the challenge of understanding complex systems. Dr. Ed Stolper, a geologist, observed, "We have genes within us that we retain from an innovation two billion years ago, and from other innovations several hundred million years ago. We have information on how the biosphere was responding to environmental changes over the last four billion years. There's an enormous amount of understanding possible if we can only figure out how to connect the biological and geological records."

Neuroscientist Dr. Edelman in turn postulated, "I believe we are going to understand how consciousness is generated. I believe that once we do understand it, we will be able to transfer that into engineering achievement." The challenges and the promises of science in the 21st century are just beginning to emerge. The W. M. Keck Foundation is honored to be in a position to observe the innovations and creativity of scientists across the nation, and internationally, as they grapple with the potential of new technologies that may transform our knowledge, and indeed, our world.

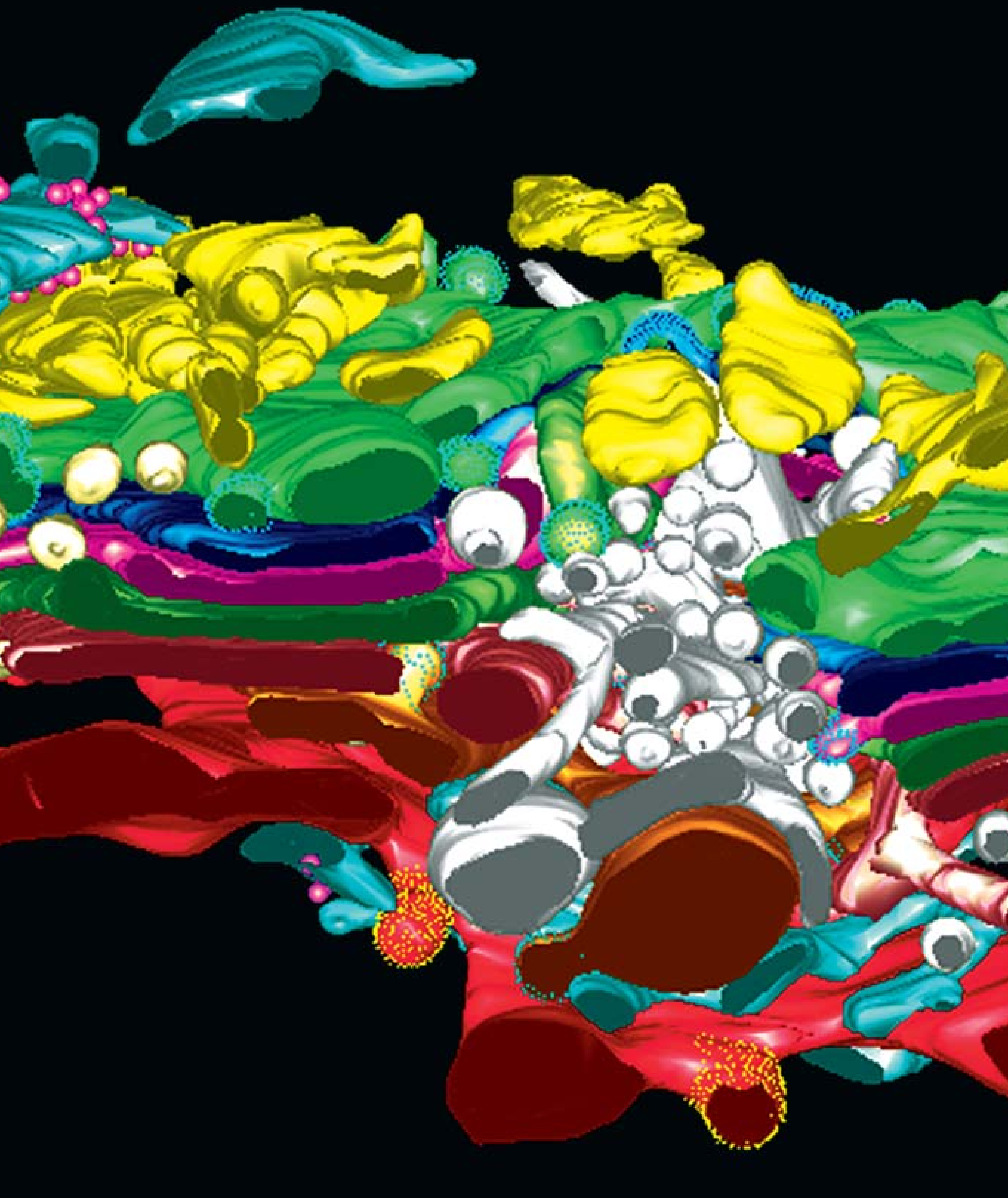
In the following four essays, Drs. Hu, Everhart, Wong, and Edelman share some of their additional thoughts on the topics of miniaturization, new technology, post-genomic biology and the "data problem," and complexity. We hope you will enjoy and deliberate on these essays, just as we at the Foundation have.

DR. GERALD EDELMAN

DR. EDWARD STOLPER

UNDERSTANDING THE DATA

Using computers, mathematics and information science to find new patterns in, and interpretations of, data will be a major challenge and opportunity for all sciences, and particularly the life sciences, in the next few decades. The image on the following page of a Golgi apparatus from a rat kidney cell was created by a computer graphics program in the Laboratory for 3-D Fine Structure at the University of Colorado at Boulder. While the Golgi apparatus' role in protein synthesis has been known for some time, the inner workings of this organelle have until now been opaque to biologists. With the help of the new program, however, the computer locates and models the edges of the membranes within the Golgi apparatus in successive slices of the organelle, eventually building up a series of contours in space. Such detailed images would not be possible without the interplay of biological and computer science techniques and expertise.



"THERE HAS BEEN LITTLE OF WHAT MIGHT BE CALLED QUALITATIVE OR STRUCTURAL, AS OPPOSED TO QUANTITATIVE, MATHEMATICAL BIOLOGY."

DR. EUGENE WONG, *Assistant Director for Engineering for the National Science Foundation*

THE STUDY OF LIVING ORGANISMS IS BECOMING AN INTERDISCIPLINARY VENTURE. BIOLOGISTS, ENGINEERS, CHEMISTS, PHYSICISTS, AND COMPUTER SCIENTISTS TOGETHER ARE DEVISING NEW METHODOLOGIES AND NEW CONCEPTUAL APPROACHES TO TACKLING THE TOUGH QUESTIONS.

THE W. M. KECK FOUNDATION STAFF

MATHEMATICS, COMPUTER SCIENCE AND INFORMATION-BASED BIOLOGY

BY DR. EUGENE WONG

INTRODUCTION

The successful sequencing of the human genome has been one of the great end-of-millennium achievements in science, and it ushers in a new era in biology. In the words of Leroy Hood: "21st century biology will be an information-based science." Genomics, proteomics, and biological pathways are but a few examples of information-centric problems that loom large in biology. The proposition articulated by Hood has major implications and opportunities for mathematics and computer science. The purpose of this short essay is to speculate on some of these.

TOOLS FOR INFORMATION PROCESSING

Dependence on information is hardly new for biology. In particular, tools to collect and represent information have always been an essential part of biology. Someone once said that there were no blind biologists because one could not work in biology without being able to look into a microscope. X-ray crystallography is a more recent but equally critical tool. Among other things, it made possible the discovery of the structure for DNA, one of the triumphs of 20th century science. Microscopy, spectroscopy, crystallography, and imaging of all kinds continue to be essential tools for biology. But these are data collection and representation tools, and their roles in biology, however important, are somewhat passive. In the new era of biology as an information-based science, tools to process information in deep and profound ways will be needed, and these are likely to come from many corners of mathematics and computer science.

Thus far, the role of computers in biology has been mostly in "computing." This may seem like stating the obvious, but I am using "computing" here in the narrow sense of carrying out numerical algorithms. These include, for example, DNA sequencing algorithms and energy minimization algorithms associated with the problem of protein folding. Computers are capable of far more than numerical computation. They are effective tools in deductive inference, in hypothesis generation, and in modeling and analysis of all kinds.

Recent applications of mathematics in biology have also largely been related to numerical computing. Combinatorics, coding, and optimization of algorithms are some of the examples. There has been little of what might be called qualitative or structural, as opposed to quantitative, mathematical biology.

PROTEIN FOLDING

Proteomics is a good example to illustrate what we might need. In its primary form, each protein is a specific sequence of amino acids connected together through chemical bonds.

"IN THE NEW ERA OF BIOLOGY AS AN INFORMATION-BASED SCIENCE, TOOLS TO PROCESS INFORMATION IN DEEP AND PROFOUND WAYS WILL BE NEEDED, AND THESE ARE LIKELY TO COME FROM MANY CORNERS OF MATHEMATICS AND COMPUTER SCIENCE."

DR. EUGENE WONG

SMALL VESICLES WITHIN THE GOLGI APPARATUS

DR. EUGENE WONG

However, proteins carry out their biological functions in three-dimensional folded structures. Because only the surfaces of the three-dimensional structure are chemically active, its folded form determines the functional behavior of a protein. In most cases, a protein folds in only one way. Hence, its biological properties are completely determined by its chemical sequence. The three-part relationship among chemical sequence, physical structure, and biological function is the essence of proteomics.

GIVEN THE SEQUENCE INFORMATION FOR A PROTEIN, CAN WE PREDICT ITS FUNCTIONAL PROPERTIES?

Conversely, given properties that one wants to realize, how do we determine the sequence, or sequences, that would have such properties? The current approach to the problem is through the study of protein folding. Grossly oversimplified, the basic idea seems to be this. A protein folds in a way to minimize free energy. Given its amino-acid sequence, how a protein folds can be formulated as an energy minimization problem. This makes it a computational problem. Once the folded form is found, the biological functions of a protein can then be studied by examining its surface.

Computing the energy minimum is a laborious task in computation. It takes a large supercomputer days to complete one folding computation. Thus, a small sub-discipline has grown around the protein folding problem: to find better algorithms, to exploit parallelism, and generally to make the computation problem more tractable. Protein folding involves interesting chemistry and generates some good problems in computing science (it certainly provides good customers for supercomputer manufacturers). But it has not yet generated good problems in mathematics. Frankly, I am surprised that certain important branches of mathematics that seem highly relevant have not yet been explored.

POSSIBLE MATHEMATICAL TOOLS

Let me speculate on some possible mathematical connections. First, it seems to me that the three-dimensional forms should be studied directly. Can the collection of all three-dimensional forms be made into a nice mathematical space of some kind, one endowed with some geometric, topological or algebraic properties? What are the operators that map one form into another? Do they form a natural structure that in turn would allow us to understand the forms? A classification of three-dimensional forms would seem useful, especially if one can thereby make use of algebraic geometry in some way.

The secondary structures: alpha-helixes, beta-sheets and beta-turns, may be embeddable in an algebraic structure, so that larger structures can be built up from basic units through the successive use of algebraic operations. Indeed, finding an algebra of secondary structures would be quite interesting. Examining the three-dimensional forms that are built up by repeated use of the algebraic operations may allow us to deduce rules of combination. Such an algebra may also give rise to effective representation of folded structures, and in turn provide a representation for the sequence-to-structure mapping.

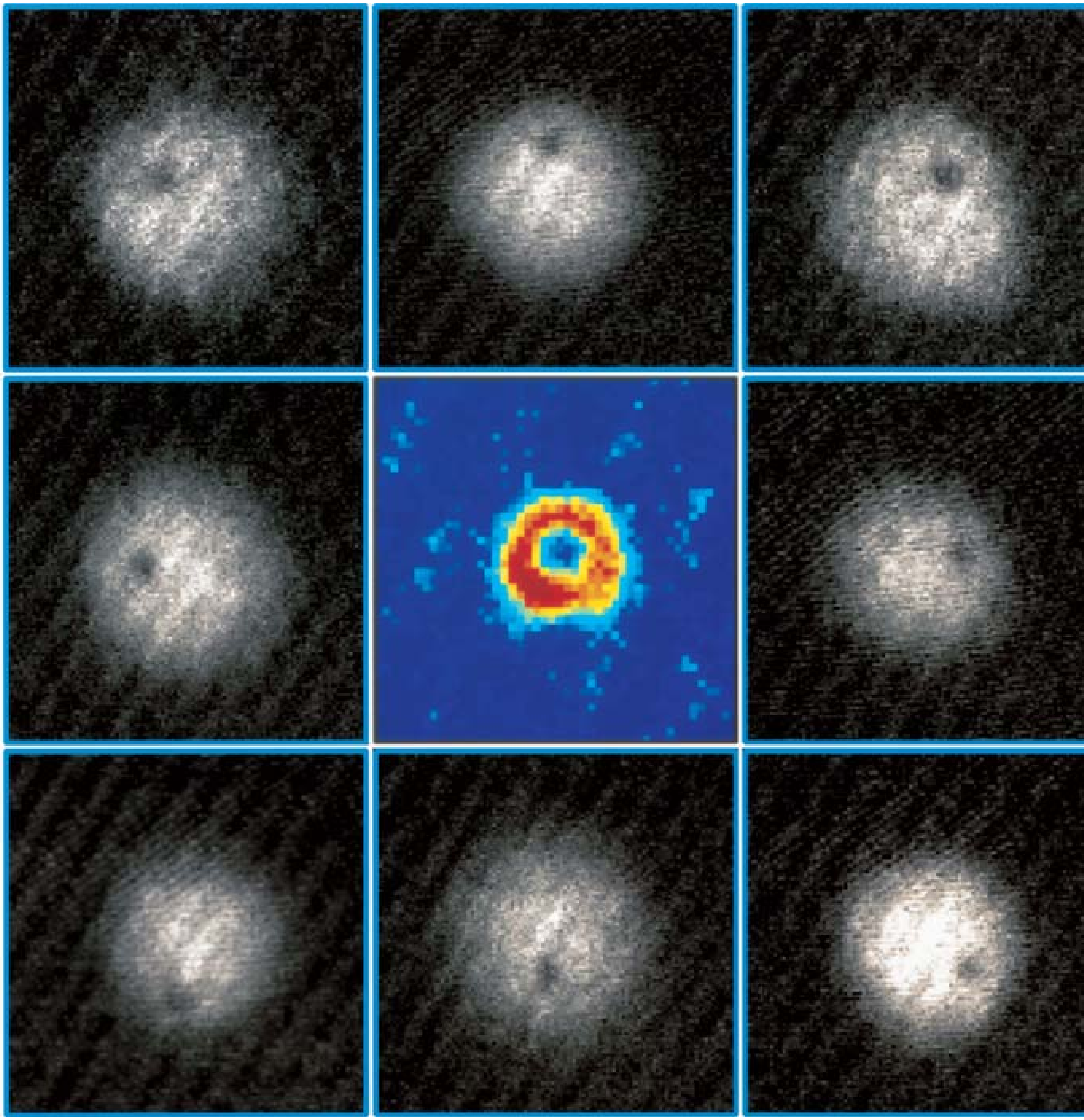
Topology and geometry would provide conceptual clarification. Algebra would provide tools for representation and synthesis, and must precede efficient computation.

Thus far, probability theory has been used mainly in connection with simulation, but some of the deepest results and most powerful techniques of probability have yet to be used. For example, evolution plays a role in all biological things, and proteins should be no exception. Does this suggest that some kind of limit theorems might be formulated? Are repeated operations that preserve some essential characteristics involved? If so, is there some kind of ergodic theorem to be discovered?

Algebra, geometry, topology, and probability theory have all demonstrated their profound power in physics and engineering. The basis for that power is deep and generic. It would be surprising indeed if they did not play a similar role in information-based biology.

NEW
TECHNOLOGY

Magnitude increases in our knowledge result directly from the development of new technologies which provide scientists with tools to probe deeper, peer farther, or ask questions never before thought possible to answer. A custom-fabricated phase-contrast microscope provided the following images of vortices in a rubidium Bose-Einstein condensate. Produced at the JILA Laboratories at the University of Colorado, the sample consists of fewer than one million atoms trapped in a magnetic field and cooled to 50 billionths of a degree above absolute zero. Under these conditions, atoms exist in one identical quantum state, an exotic form of matter predicted by Satyendranath Bose and Albert Einstein over seventy years ago. The central image shows the vortex as it drifts under the combined effects of pressure gradients and the Coriolis force, much in the way a tornado might wander across the cornfields of Kansas. This "quantum tornado" could itself lead to further new technologies such as atom lasers or quantum computing.



THE PREDICTIVE POWER OF SCIENCE IS POISED FOR AN UNPRECEDENTED LEAP FORWARD, AND THE SPRINGBOARD FOR THIS JUMP WILL BE THE RAPID ADVANCE OF TECHNOLOGY. NEW TOOLS COUPLED WITH NEW THEORIES TO GUIDE THE PROCESSING AND UNDERSTANDING OF DATA COULD LEAD TO A DEEPER UNDERSTANDING OF NATURE, AND IMPROVE OUR ABILITY TO DEVISE SOLUTIONS TO NATURE'S MYSTERIES.

THE W. M. KECK FOUNDATION STAFF

NEW INSTRUMENTATION ADVANCES SCIENCE

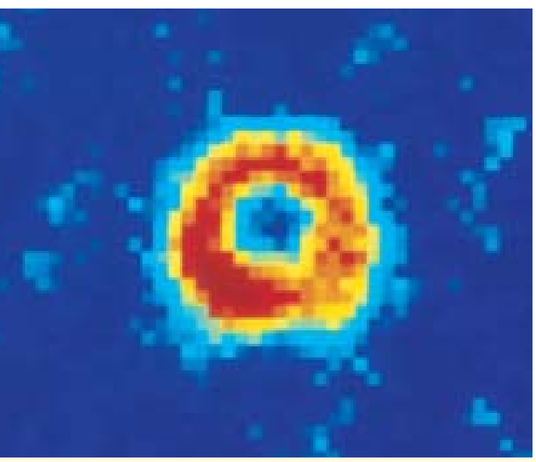
BY DR. THOMAS EVERHART

While it is generally recognized that advances in science depend upon new instrumentation developed to solve particular problems or to investigate particular phenomena, the reason for this is not often discussed. I believe there is something very fundamental about increasing our ability to measure any dimension to new precision. Microscopes allow us to see what the unaided eye cannot. Telescopes bring objects we cannot resolve closer so we can inspect them. Oscilloscopes have allowed us to view the dimension of time in shorter and shorter increments, and radioactive dating has permitted us to know much more exactly the age of rocks, fossils, and other ancient items of interest. Sometimes instruments allow us to see through opaque objects,

"RECENTLY, THE DEVELOPMENT OF THE INTEGRATED CIRCUIT AND THE RESULTING IMPROVEMENT IN THE SPEED OF COMPUTATION AND COMMUNICATION HAVE MADE NEW WAYS OF DOING SCIENCE POSSIBLE."

DR. THOMAS EVERHART, *President Emeritus of Caltech, and Senior Scientific Advisor to the W. M. Keck Foundation*

A FALSE COLOR IMAGE OF THE VORTEX IN A BOSE-EINSTEIN CONDENSATE



DR. THOMAS EVERHART

using X-rays, positrons, and more recently, the magnetic resonance of nuclei inside objects like our bodies. The use of such instruments normally changes our perception of what we "see." This new perspective often resolves problems that we posed or suspected, and sometimes challenges us with new problems that previously we could not imagine. This has been true with the magnifying glass, the light microscope and telescope, X-rays used in either shadow imaging or diffraction, the transmission, reflection, and scanning electron microscopes, and more modern instruments based on acoustical waves, lasers, magnetic resonance, and Auger electrons. The scanning tunneling microscope and the atomic force microscope extend our sense of touch to much smaller dimensions, but present the information as a visual image, hence they are called microscopes.

Recently, the development of the integrated circuit and the resulting improvement in the speed of computation and communication have made new ways of doing science possible. Hypotheses can be tested by simulation based on models, often raising questions not suspected, and suggesting avenues of research that would have been missed. Data can be taken much more rapidly, using sensors and electronics that have only recently become available. By using many sensors, parallel streams of data provide insights that the single measurements and point-by-point plotting of earlier generations could never give. This not only speeds up the progress of science, but enables science that could not have been done before. In fact, so many variables can now be measured simultaneously that an entirely new field, complexity theory, has developed.

These changes brought about by modern electronics, as embodied in instruments, computers and communication, are changing many areas of society: business, education, government, and the home. They enable information to be disseminated more rapidly to the public, and enable individuals to be in much more rapid communication with each other. This fact alone has speeded the progress of science, allowing more distant collaboration by colleagues in different institutions, sometimes in different countries. But in addition, other advances have enabled instruments to be constructed or located where they are much more effective.

An obvious example is the Hubble Space Telescope, located above the atmosphere to overcome the limitations of random diffraction and scattering of light by the atmosphere. Another example is the Keck Observatory, which is located at one of the best astronomical observing sites on the surface of the earth. The 36 lens segments composing each of the Keck ten-meter telescopes are constructed of new materials, positioned by more accurate sensors, and adjusted by computers that are essential for its performance. The Hubble and the Keck instruments have provided us with a wealth of new insights. They have changed our perception of the universe, and therefore have provided us an altered view of our own existence.

No less striking are the advances that instruments have enabled in biology and medicine. Two decades ago, a team of Ph.D. researchers spent half a year analyzing the sequence of a single gene. Due to the development of gene analyzers and sequencers, today a technician can do far more work in an afternoon. Indeed, we expect to have a good first approximation of the entire human genome completed during the year 2000. The fundamental understanding of biology that has led to this accomplishment has profound implications for human medicine. Further advances can be expected as chemists and biologists improve their understanding of the molecules that make up living organisms, and as new instrumentation becomes available to speed our knowledge of genetics and what implications our genetic composition has for our health. New diagnostic tools being developed based on this new understanding will revolutionize how medicine is practiced during the next decade.

New instrumentation has also improved our knowledge of neural processes. We are learning more about how neurons interact, where cognition takes place, and some scientists are even starting to probe the questions of consciousness. Perhaps the ultimate questions are those posed by individuals who think about how people think, what it means

"THE KNOWLEDGE GAINED FROM THESE INSTRUMENTS STIMULATES SCIENTISTS TO DEVISE NEW EXPERIMENTS, TO ORIGINATE NEW THEORIES AND TO TEST NEW MODELS THROUGH COMPUTER SIMULATION."

DR. THOMAS EVERHART

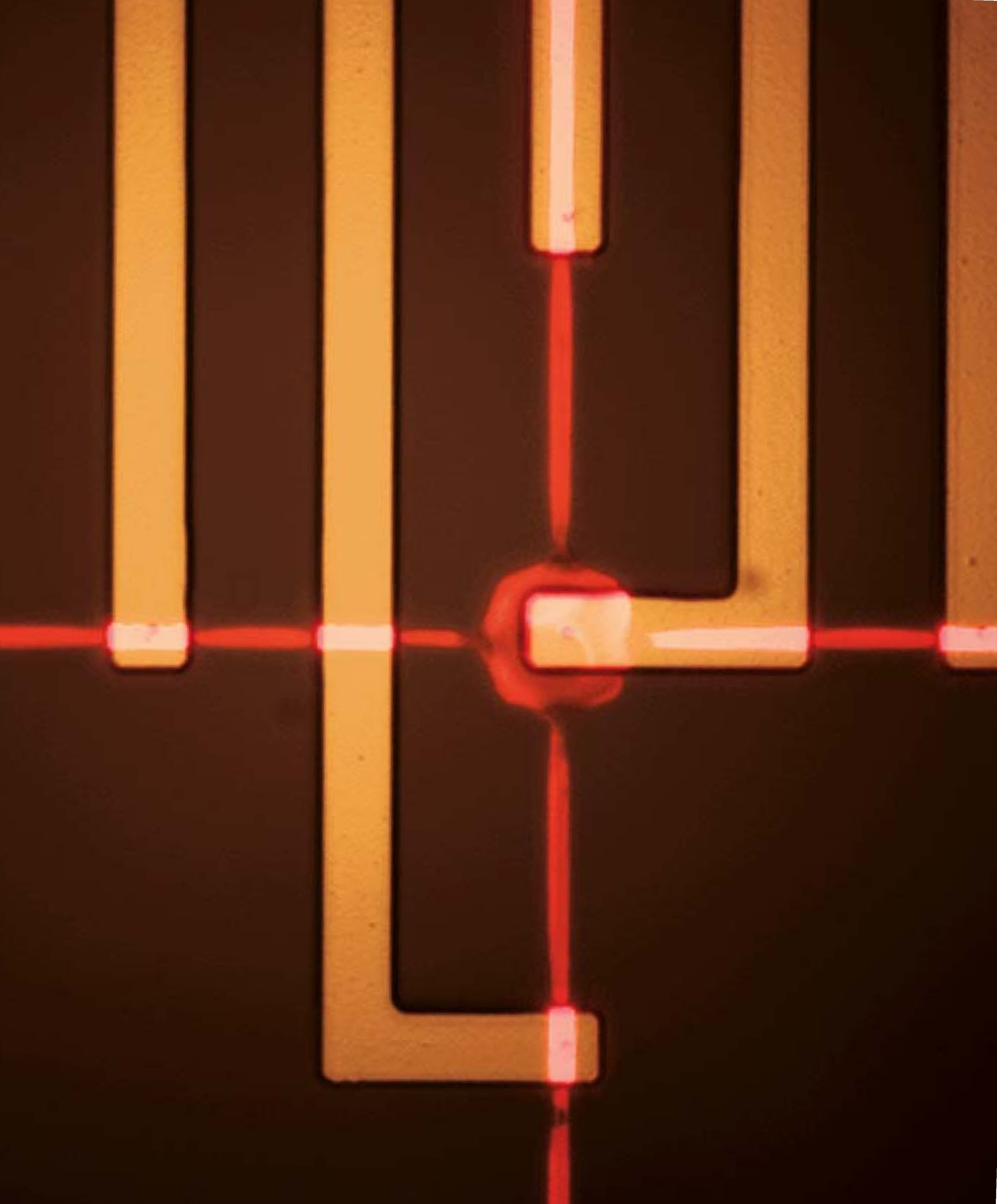
to be conscious, and how better knowledge of these topics can be used to improve the human condition.

Chemists have used the techniques of sampling to deduce what is happening during chemical dissociation or bonding. Using one laser pulse to stimulate a molecule, and a second to observe the effect of the stimulation, the dynamics of chemical reactions have been probed with a time-resolution that was unthinkable a few decades ago. By using very short pulses with a duration measured in femto-seconds, and a separation between the exciting pulse and the observing pulse measured in tens of femto-seconds, molecules have been "caught in the act" of dissociating. The Nobel Prize for Chemistry was recently awarded to Dr. Ahmed Zewail who received seed support for such work through a grant from the Keck Foundation.

New instrumentation is extending our senses, providing us observations of smaller dimensions of length and time, and extending our ability to see farther out into the universe, and hence farther back in time. At the same time, we are learning to use new signals to observe atoms, molecules, and cells, sometimes *in situ* and non-invasively. The knowledge gained from these instruments stimulates scientists to devise new experiments, to originate new theories, and to test new models through computer simulation. The power and speed of our instruments and computers continue to improve the rate at which scientists learn about the natural world, and engineers invent new devices and processes that improve the human condition. Such instruments devised by people who want to solve problems are key to the further advancement of knowledge.

NANO-MINIATURIZATION

Miniaturization has proceeded from the milli- through the microscales, and is now venturing rapidly into the realm of the nanometer. Nanometers are ten Angstroms, or one thousandth of a micrometer, which itself is the size of an average bacterial cell. The nanobiotechnology program at Cornell University is focused on the development of micro-miniature devices and machines for use in biological research. The following image shows a pattern of one micrometer-wide fluorescently labeled polylysine (narrow lines) aligned to a pattern of five micrometer-wide gold electrodes (wide lines). Generated by contact printing, these patterns can provide precise geometric arrays of proteins and antibodies for directing cell growth and attachment on silicon substrates.



"WE MAY BE ABLE TO DESIGN SOPHISTICATED, FUNCTIONAL DEVICES WHOSE TOTAL DIMENSIONS MAY ENCOMPASS THE SIZE OF A CUBE ONLY A FEW ATOMS ACROSS."

DR. EVELYN HU, *Director of QUEST, an NSF-funded Science and Technology Center, and Director of the NSF-sponsored National Nanofabrication Users Network*

VISIONS FOR APPLICATIONS OF MINIATURIZED SENSORS RANGE FROM A LAB IN A BOX TO A COMPUTER ON A CHIP. TO REALIZE THESE VISIONS, HOWEVER, THERE IS A NEED FOR A NEW PARADIGM GOVERNING BOTH THE ARCHITECTURE AND TECHNIQUES INVOLVED IN MINIATURIZATION.

THE W. M. KECK FOUNDATION STAFF

WHAT ARE THE NEXT CONCRETE STEPS TO CREATING FUNCTIONAL NANOSCALE DEVICES?

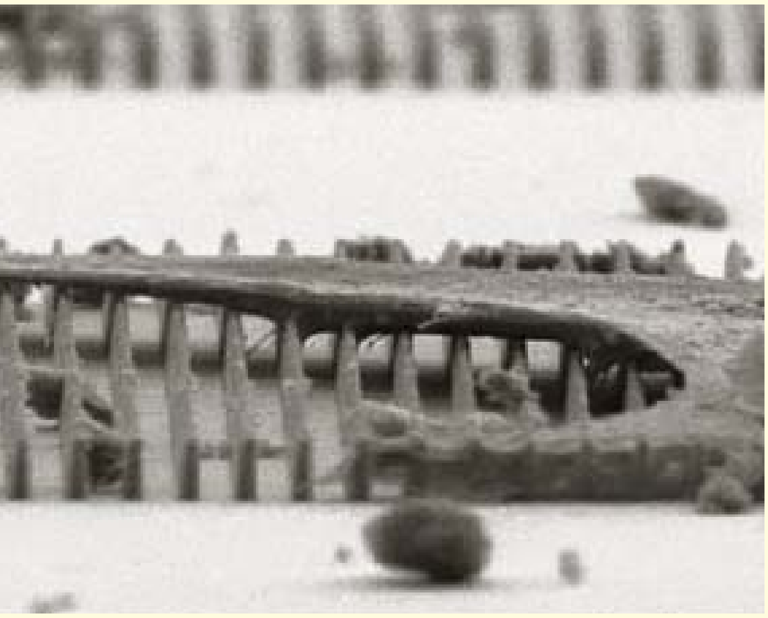
BY DR. EVELYN HU

Our ability to manipulate and control structures at the nanometer scale makes possible the engineering of materials and material properties from the "ground up." As form can and does often determine function, control at the nanometer scale allows us to tailor electronic, magnetic, and optical properties – in other words, we may be able to design sophisticated, functional devices whose total dimensions may encompass the size of a cube only a few atoms across. Using such electronically functional nanometer building blocks (or devices), we then have the possibility of constructing complex systems of devices that are capable of rapid transmission of information, sophisticated decision making, and response on a very local spatial scale.

In fact, one could argue that it is only by combining such nanodevices into systems that one truly takes advantage of the scaling inherent in nanoscale devices. It is the complexity required of such sophisticated systems, together with the precision and perfection of the component nanometer structures, that pose the greatest challenges in establishing a true nanoscale device technology. An example of a nanometer-scale building block system found in nature is a biological cell. Speaking of this, Gerald Edelman commented, "…the complexity of this system is dazzling, and is certainly not one an engineer would put together at any reasonable economic expense." Indeed, although there are currently tools and techniques available that can create individual device elements at the nanometer scale, such techniques are both too costly in time and too imprecise in the delineation and placement of the nanostructures to be at all viable. In recent years, there has been substantial interest and time invested in the exploration of individual nanoscale devices: Coulomb blockade devices, electronic quantized conductance, optical devices utilizing quantum dots, demonstration of controlled switching in molecular devices. The important next challenges are linking up two and then more devices to carry out a reliable transfer of information, or to perform a computation. Accessing levels of greater complexity in a true nanoscale technology requires important advances in fabrication, characterization and system architecture.

One important step in realizing a true nanoscale device technology is therefore the exploration of alternative fabrication techniques that would accommodate both precision and perfection at the nanometer scale, and provide for the extensive set of device interconnections and attachments that would form a functional system or circuit. Researchers are already pursuing a number of "self-assembling" techniques where the natural coding built into the fabrication process itself ensures that the requisite tolerances on the structure size and perfection will be met. This self-assembly must extend to different size scales as we take the building block components and link them together into

ASTROCYTE CULTURED ON SILICON PILLARS



MEMBRANE PATTERN ETCHED INTO SILICON SUBSTRATE

DR. EVELYN HU

"LOOKING TO THE EXQUISITE SELECTIVITIES AVAILABLE IN NATURE,

RESEARCHERS HAVE BEGUN TO EXPLORE LINKS BETWEEN BIOLOGICAL MOLECULES AND INORGANIC ELECTRONIC MATERIALS."

DR. EVELYN HU

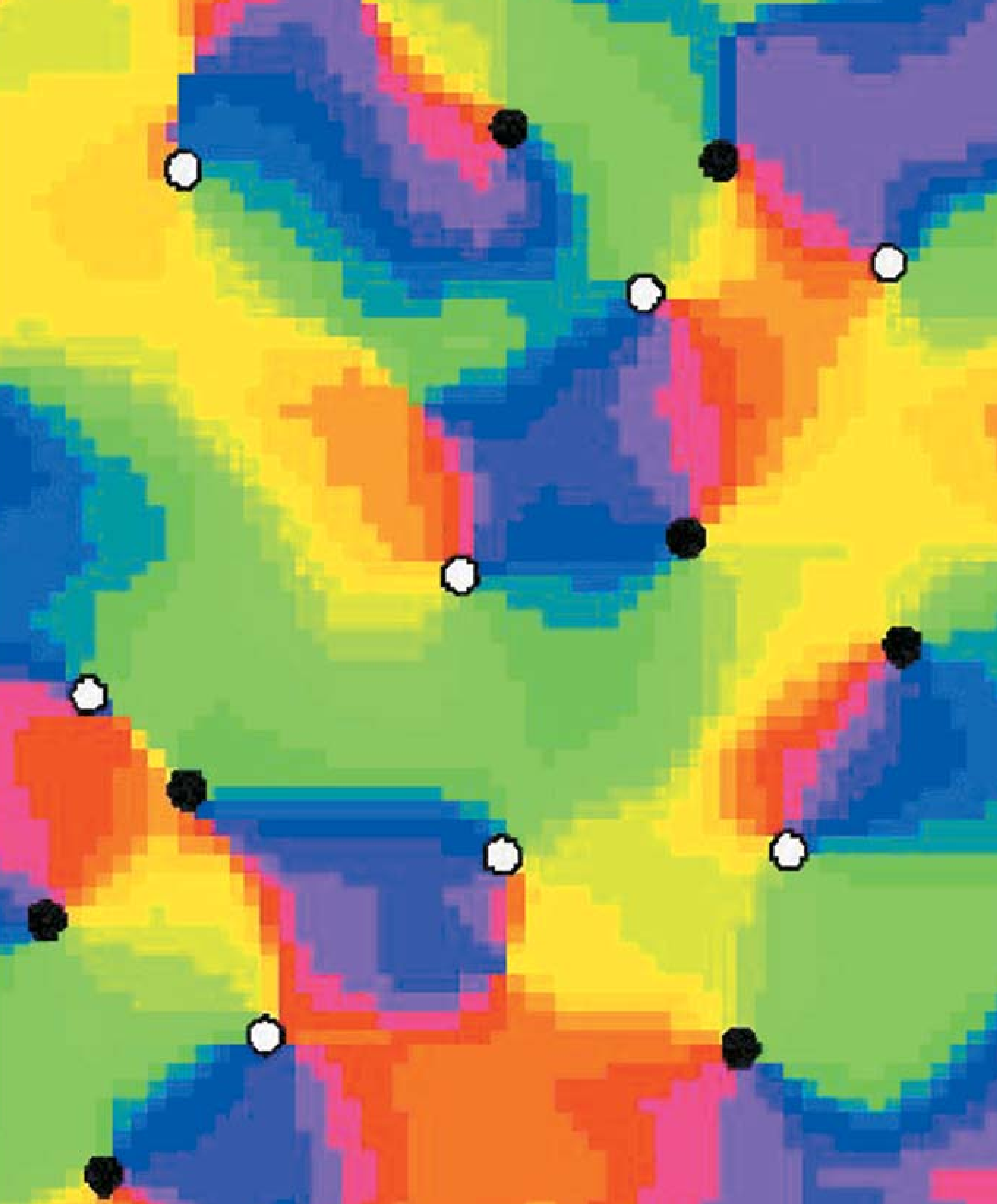
a hierarchy of structures of increasing complexity. Looking to the exquisite selectivities available in nature, researchers have begun to explore links between biological molecules (proteins, DNA, etc.) and inorganic electronic materials (metals and semiconductors), attempting to use the biological molecules as the agents of assembly of the electronic materials. The new techniques will almost certainly be generated from the interfaces of disciplines such as electrical engineering, physics, biochemistry, and materials science, and thus the mastery of such techniques will require sufficient understanding of the component disciplines.

There must be adequate means of characterizing the properties of both the nanoscale building block devices and their larger-size, linked constructs (circuits, systems), ideally in an *in situ* manner in order to monitor the assembly process. Many of the individual tools already exist. For example, scanning tunneling microscopes allow sensitive probing of electronic properties at the nanoscale. There are a host of other "scanning probe" tools that will allow similar nanometer-scale characterization of optical, magnetic and structural properties. Again, there will be challenges to extending such characterization from an individual nanoscale device to more complex circuits and systems.

Finally, and in many ways most importantly, there must be a parallel effort invested into the design of new device and system architectures that will better map onto, and take advantage of, the nanoscale size of the system components. The optimal conditions for signal processing and transmission in integrated circuits are dramatically different from those pertaining to biological systems. Nanoscale devices that are judged by present-day electronic device standards of signal strength, operating temperature, cost of fabrication, etc., will inevitably be found wanting. The identification of new architectures (ways of arranging the nanoscale devices and routing their signals) may allow us to mitigate the requirements of absolute structural perfection and homogeneity of size and composition; and provide us with powerful new means of signal processing and information transfer not accessible to current-day electronic circuits.

COMPLEXITY

All natural phenomena are the result of a complex interplay between the internal organization of an object or organism, and the various features of its environment. Unraveling these intertwined threads is a challenge to all scientists. The following colorful image, provided by the Center for Magnetic Resonance Imaging at the University of Minnesota, is a composite-angle map which shows the orientation preference of columns of neurons in the cat visual cortex. These neurons, in their distinctive "pinwheel" structure, react only to a portion of an image having a very specific orientation (straight up, or 45 degrees to either side, for example.) Is this preference learned and selected through a kitten's interaction with its environment, is it innate, or a combination of the two factors? Neuroscientists are trying to understand these and many other questions about how something as complex as the brain works.



HOW DO WE BEGIN TO UNDERSTAND COMPLEXITY IN A SOPHISTICATED WAY? THERE ARE VAST AMOUNTS OF DATA TO BE SORTED, INDEXED, CATALOGUED, ANALYZED AND SYNTHESIZED. THERE ARE NOW CONCEPTUAL APPROACHES TO BE DEVELOPED, AND THESE THEORIES WILL IN TURN INFORM AND REFINE THE NEXT GENERATION OF EXPERIMENTS.

THE W. M. KECK FOUNDATION STAFF

COMPLEX DYNAMIC NETWORK INTERACTIONS

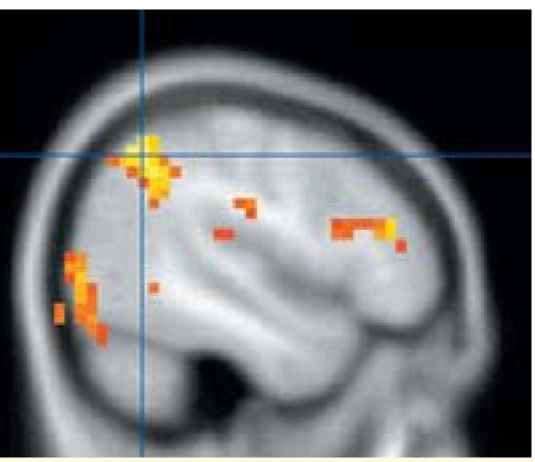
BY DR. GERALD EDELMAN

At a certain time in the history of biology – roughly the end of the 19th century – it first became possible to view the living cell as a machine. This new perspective, stimulated by the application of biochemistry to physiological problems and to some extent by an increasing grasp of genetics, flourished until the late 1950s.

This view of the cell achieved much: the analysis of metabolism in terms of defined cycles, the relation of cellular structures to such cycles, the analysis of the chemical nature of the gene and of proteins, the analysis of biochemical signal paths, and finally, the remarkable explosion of molecular biology. At that time, one could comfortably take the position that, to have a satisfactory picture of living processes, it would only be necessary to extend the deterministic picture of chemical causes to increasing numbers of biological components.

"COMPLEXITY PRINCIPLES, IF FOUND TO BE GENERAL, WILL ALLOW US TO CONNECT SYSTEMS OF DIFFERENT COMPONENTS INTO CAUSAL NETWORKS RELATING STRUCTURE, FUNCTION, AND EVOLUTION."

DR. GERALD EDELMAN, *Director of The Neurosciences Institute and President of The Neurosciences Research Foundation*



ACTIVATION MAP OF THE HUMAN BRAIN, DARTMOUTH COLLEGE

DR. GERALD EDELMAN

As more and more components and interactions were studied, however, a certain uneasiness gradually began to emerge. Genes do not specify proteins independent of context, and they could sometimes yield unexpected interactions or even be removed with no major consequences. Signaling pathways appeared to work within complex parallel networks. Subtly different forms of proteins could have very different physiological functions. Biological phenomena involving completely different structures yielding the same output became more evident. In complex multilayer systems such as the brain, extensive variance in anatomy and dynamics was found to possess extraordinary compensatory capability.

Such observations increasingly undermined notions that biological systems obey linear principles and that their deviations from simple causal chains were simply "noise." To an evolutionist, the emergence of stochastic, non-linear properties would perhaps not be surprising inasmuch as natural selection operates on variant populations to sweep in any complexities that contribute to fitness.

But the problem remains: how should we proceed to gain a better understanding of the non-linear causal connections in biological systems which range in complexity from sub-cellular organelles to exquisite physiological entities like the central nervous system? This problem cannot be reduced simply by mathematical analysis, important as that is. More and more, the notion of complex networks has come to the fore: networks of signaling molecules, networks of genes, networks of cells in tissues, and most intricate of all, networks of neurons in the brain. And, of course, it did not escape notice that dynamical network interactions of great complexity also occurred in ecology, in animal communication, and in human social chains.

Biological complexity necessarily involves huge numbers of components, as well as historical influences leading to individuality and parallel causation. Moreover, the different layers of biological systems – molecular, cellular, systemic, organismal, and social – do not operate independently of one another, but instead act in an intricately intermeshed fashion to generate emergent phenomena.

To deal with these issues in a meaningful fashion requires that we develop a theory of complex systems. To accomplish this will require an approach to systems modeling that fosters the application of principles of complexity to a large variety of different physiological and chemical mechanisms.

How might we go about achieving such a goal? I believe that there are a number of components in any adequate modeling strategy:

1. Development of a complexity theory that goes beyond that developed by computer scientists for algorithmic strings.
2. Incorporation of complex multilevel interactions in computer models of biological systems.
3. The continual interaction between experimental methodologies and appropriate revisions of the computer models.
4. Construction of synthetic models of physiological systems embedded in real world devices.

I believe that by coordinating these components, a set of general principles can be derived to account for biological complexity, despite the fact that mechanistic causal analyses often differ greatly among different biological systems. I turn here to two contrastive examples that point up both the promise and difficulties of such a program.

Consider a single cell and its signal transduction networks. We know that a major mechanism of signaling events is phosphorylation of certain proteins by enzymes called kinases and dephosphorylation by other enzymes called phosphatases. There are roughly 2000 different kinases and 1000 different phosphatases in a single cell. How can we gain a general understanding of the principles by which binding of a protein, a hormone, or a drug on the cell surface can alter gene expression in the cell nucleus? Experiments to identify protein components of the signaling pathway clearly are necessary. But, in the end, the most convincing way of composing a picture of parallel causal chains involving more than two or three molecular types would be to model the system in a computer, changing various components, sequences, and orders of events.

"DO THESE DISPARATE SYSTEMS – THE CELL AND THE BRAIN – FOLLOW SIMILAR PRINCIPLES OF COMPLEXITY?

I BELIEVE THAT, TO A GREAT EXTENT, THEY DO."

DR. GERALD EDELMAN

Such a computer model can then guide an experimental test of the consequences of signaling events. It is possible, however, that the domains of as many as ten different proteins all interact statistically within tenths of a second to block a given highly specific path to the nucleus. At present we have no known method of measuring such interactions in real time. What would be required is an optical means for analyzing multiprotein interactions in short periods within a single living cell – certainly a challenging state of affairs for the experimentalist and the systems modeler.

Turn now to an even more complicated system comprised of cells and tissues having an enormous connectivity and integrated dynamics: the central nervous system. Here we run into a hopeful paradox. Because the brain has a more or less stable and defined neuroanatomy that is critical to its behavior, we can study its system dynamics by modeling its actual functional connectivity. The problems of its component cells remain the same as for those for the hypothetical cell discussed previously. But now we can average over the multiple cellular states to model neural dynamics, following a theory of how such a multilevel system might operate.

The paradox is that we presently are in a better position to achieve this than we are for an individual cell, both for instrumental reasons and for reasons having to do with intrinsic anatomical structure. Indeed, quite intricate models of brain systems integrating neuroanatomy, neurophysiology, and biochemistry have already been constructed with insightful consequences. There have even been synthetic neural modeling programs leading to the construction of non-living devices that incorporate our knowledge of neural structures and function and that actually can be conditioned and learn.

Do these disparate systems – the cell and the brain – follow similar principles of complexity? I believe that, to a great extent, they do. What do they have in common? Each is composed of multiple levels of organization. At the lower levels, each contains many structurally different heterogeneous components with different functions. At higher levels, such components interact and share mutual information leading to increasing degrees of integration. A theory of such systems has already been formulated that can quantitatively assess complexity as a reflection of both the independence of smaller component subsystems and the interdependence of larger subsystems.

One intriguing property of these complex systems is that if one such system responds to signals of another independent system and reflects the statistics of that second system, the complexity of the first system increases. Another remarkable property is degeneracy: the ability of structurally different network paths in a complex system to give rise to the same output. This is seen in gene networks, in the central nervous system, and in immune networks. Recent explorations suggest that increases in degeneracy are accompanied by increases in complexity. In fact, this property may account for the increase in complexity over evolutionary time: natural selection would favor degenerate systems because of their compensatory properties and thus would lead to an increase in complexity.

What may we expect the future to bring? One answer is clear. Computer hardware will make it possible to simulate systems of millions of components. Complexity principles, if found to be general, will allow us to connect systems of different components into causal networks relating structure, function, and evolution. Synthetic approaches, in which computer modeling is linked to the behavior of real world devices, will enable deeper insight into complex physiological systems ranging from developmental pathways to complex hormonal and brain functions. Finally, such efforts should drive new inventions – both of analytical tools and of practical devices. While not excluding classical methods, system modeling promises greatly to enrich the repertoire of approaches to the unification of biology.

THE HUMAN ASPECTS OF DOING SCIENCE

THE HUMAN ASPECTS OF DOING SCIENCE

A SUMMARY OF THE ROUNDTABLE DISCUSSIONS COMPILED BY THE W. M. KECK FOUNDATION STAFF

Our panelists shared a belief in the power of science to find the answers to questions that will profoundly affect our way of life in the 21st century. They also shared a concerned recognition that the way science is currently supported, and research is performed, profoundly affects whether or not and how those answers will be found.

The discussants focused on a number of specific and interrelated issues that arose over the course of the roundtable discussions. The most fundamental of these was the problem of how to spark the scientific spirit – how to expose talented young people to the "joy of discovery" before they are lost to the sciences. Other issues that inspired lively debate included the best ways to facilitate true inter- and multi-disciplinary research, and effective avenues for supporting development of new technologies.

THE "PROTOPLASM" COMPONENT

What is the single most important ingredient in a successful scientific enterprise? Our panelists all agreed; it is the people themselves. People conceive new ideas, methods, and questions, and people perform the painstaking work required to investigate them. Dr. Shirley Tilghman described it best: "I'm a big believer in human protoplasm," she said emphatically, "because that's where serendipitous discoveries are going to come from."

The term "protoplasm" quickly became the shorthand description for this most unpredictable element in the scientific process. The key question, then, as elucidated by the discussants, is how to both identify and encourage good young protoplasm to enter science, to facilitate their research. One critical period for scientists is during their early careers, first as postdoctoral fellows, and later as young faculty members. Encouragement and financial support are invaluable at this time. "I've reached an age," Dr. Ivan Sutherland observed, "where people call me and say will you accept such-and-such an award or such-and-such an honor. It has struck me, however, that the most important award or honor I've ever received was a National Science Foundation fellowship to graduate school." Dr. Sutherland goes on to explain what was so important about that award. "I've come to think of prospective and retrospective awards as different in character. Retrospective awards honor people who have accomplishments that are easy to see. Prospective awards make it possible for young people with promise to achieve their promise, and I think the prospective awards are far more valuable to society than the retrospective ones. Unfortunately it's much harder to identify appropriate recipients."

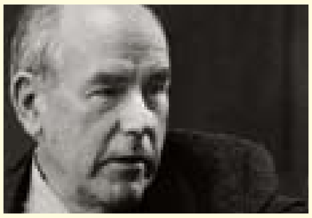
The panelists agreed that the transition from student to faculty member and independent researcher is a crucial time in the life of a scientist. As the system works now, this transition is, at best, difficult. Explained Dr. Tilghman: "I have spent 13 years watching assistant professors at Princeton come in and suddenly be faced with an extremely diverse and demanding set of job requirements. This is independent of getting a laboratory started, getting a project going, and getting funding. I'm coming close to the conclusion that it doesn't compute. This really is a system that is almost at the breaking point." Dr. Tilghman proposed a model in which young faculty are relieved of teaching and administrative responsibilities for the first few years of their research career.

Dr. Kip Thorne agreed that a similar problem exists in the field of physics, especially theoretical physics in which the best young scientists can make major discoveries in the first few years after the Ph.D. He proposed a "senior postdoctoral structure" that would provide "six years of stable support without other major responsibilities, so that young investigators can make their mark and have a real impact in fundamental physics."

It is in this spirit of encouraging young people at a very critical and creative time in their careers that the W. M. Keck Foundation initiated in 1998 the Distinguished Young Scholars in Medical Research Program. Designed to foster the careers of some of the nation's best and brightest young investigators, Young Scholars provides five years of research support for scientists who are no more than four years into their first tenure-track position. The program is now in its second year. Work by two of the members of the first-year class of Young Scholars, Dr. Partho Ghosh and Dr. Phyllis Hanson, appears in this book. We look forward to watching their careers and research develop, and we are equally interested in our other three no less illustrious Young Scholars, Dr. Bruce Clurman, Dr. Judith Frydman, and Dr. Mark Gerstein.

Another "protoplasm" issue discussed by the panelists is the need for alternative education tracks. While in the natural sciences we most often concentrate on educating Ph.D.s, or M.D./Ph.D.s, there is an increasing focus on re-legitimizing other degrees as a goal, in particular the master's degree. Although some disciplines, such as engineering, have always recognized a master's degree as sufficient training for taking a leadership role, in the biomedical and other fields it has become primarily a signpost on the way to a Ph.D. To address just this issue, the Keck Graduate Institute of Applied Life Sciences (KGI), will train scientists interested in both the practice and management of applied life sciences in fields such as computational biology and biomedical engineering. The degree the students will earn has been described as more like an M.B.A. than a traditional Ph.D. A number of such programs have recently been initiated, though none in a freestanding institution such as KGI. The Foundation feels that the freedom afforded there is necessary to facilitate the implementation of an innovative and effective curriculum and infrastructure.

DR. SHIRLEY TILGHMAN



DR. IVAN SUTHERLAND

"I'M A BIG BELIEVER IN HUMAN PROTOPLASM."

DR. SHIRLEY TILGHMAN

DR. KIP THORNE

DR. HERB PARDES

Dr. Herb Pardes pointed out another important problem when he noted that young scientists need more than research funding. They require an institution that provides a supportive infrastructure that includes not only lab space and equipment, but also intellectual capital and administrative leadership. Dr. Pardes encouraged the panelists to consider participating in future discussions on "what allows the creative process to go forward and frees young people to do constructive work." He and others cited variables that should be investigated in more detail, in areas ranging from effective architectural designs for facilitating inter-disciplinary work to the need for flexibility in the tenure process.

COMMUNICATING SCIENCE: THE JOY OF DISCOVERY

Freeing talented and creative investigators to do constructive work is only one layer of a multi-layered problem. The roundtable participants on both coasts emphasized a more basic problem: capturing young peoples' interest in science early in their education. Many bright young people turn away from thinking about a career in science, "because they don't see how exciting and interesting it is," said Dr. Tilghman. "And that's because we're not teaching it, in my opinion, in a way that reveals why we feel so passionately about science. I see a major challenge for science education at all levels, with the focus needing to be on the joy of discovery." Our panelists all said that what caught their attention as students, and persuaded them to become scientists, was the "rush" that comes with a scientific discovery. "I think we have a great story; we're just not telling it," concluded Dr. Tilghman.

Dr. Pardes echoed these sentiments, and added an additional concern: "One of the most formidable problems in this regard is that there are very large populations of people in this country who are under-represented in science and who are not coming into the field. It's a whole population lost." He suggested framing the question this way: "How do we study and understand the ways in which the excitement of discovery comes alive in all young people?"

The W. M. Keck Foundation recognizes the critical role that undergraduate education plays in nurturing young scientists. It continues to support curricular innovation and student-faculty research in science and engineering at institutions focused on undergraduate education, particularly liberal arts colleges.

FACILITATING MULTI-DISCIPLINARY RESEARCH

The complexity of the issues facing scientists today demands collaborative, innovative approaches. Many panelists felt, however, that the current administration of science, from departmental lines in universities, to the study group review method favored by governmental funding agencies, was unable to encourage this type of work. This is an area where risk-taking and flexible funding, from foundations or other sources, was seen as invaluable.

"We talk a lot about inter-disciplinary, and even multi-disciplinary science," mused Dr. Lee Hartwell, "but it's hard to point to good examples where this kind of integration of disciplines is happening. I don't think that the answer is training renaissance people who are experts in more than one field. There's a lot to be gained by creating environments where people can collaborate and talk to one another and learn enough outside their own discipline to be conversant. We seldom create such environments or such training opportunities." Again, this was cited as an area in which we are not even sure which environments are most conducive to facilitating the kind of interaction prized by the proponents of inter-disciplinary research. Many panelists noted that further study of this issue would be useful.

Lack of communication also constrains inter-disciplinary approaches to problems. The majority of today's scientists

DR. LELAND HARTWELL

DR. CLAIRE MAX

were trained in a deep, single-discipline curriculum. This makes them extremely effective in their field. When scientists in different fields wish to work together, however, the first problem they often face is simple communication. Like two people speaking in different tongues, they must establish a common language before real collaboration can begin. The scientists then often find that their collaborators are not only their partners, but also their teachers. The debate has only begun on how to teach the next generation of scientists so that they are familiar with the tools and problems faced by other disciplines.

As Dr. Marvin Cassman notes, "the concept of inter-disciplinary research is something that's been kicking around for a long time. The key is training. You can do some things with today's scientists, but I think many of them have perceptions and training and background that make it difficult for them to operate easily in an inter-disciplinary mode. That doesn't mean it can't happen, or that you can't stimulate it in the future, but if you really want it in the future – I'm talking about six to ten years from now – you need to find some way to make inter-disciplinary training the reality. I haven't seen that yet except on very rare occasions."

Many multi-disciplinary efforts require the collaboration not only of scientists from different disciplines, but often from multiple institutions as well. Dr. Thorne cited the LIGO project, which is endeavoring to measure gravitational waves, as one successful model for such large programs. This ambitious undertaking would simply not have been possible without the cooperation of many researchers at geographically distant sites and from diverse sub-fields of engineering and physics. Dr. Claire Max concurred that to solve many problems, we need more groups that are larger than the traditional professor-plus-students. "There is a chance here to build a new paradigm for collaborations. I think foundations can provide incentive for some of these interactions."

Dr. Thorne noted that to be successful, the sociological components governing the make-up and management of such research need to be considered. He pointed out the clear need for institutions to plan how to educate scientists to be prepared to take the leadership roles in large projects. Dr. Sutherland concurred. "Leadership is a very strange phenomenon. How do you find people that others will trust to make the key decisions?" he queried. Several panelists suggested that conferences or studies concentrating on what constitutes effective management of intermediate-scale collaborations would be useful, and that foundations could play a role in facilitating this work.

Finally, in addition to training and administrative issues, the panelists agreed that funding the development and dissemination of new technologies is critical to the advancement of science. Each new generation of instruments allows an order of magnitude leap forward in our ability to get the answers to previously unasked questions. Each leap is technology driven. As one example, Dr. Sutherland noted the opportunities to "promote the course of science by building specialized information machines that are appropriate to investigating a particular problem." For instance, a computer designed to mine specific databases of protein structures or of an all-sky telescopic survey, would be a cost-effective way to handle a major information problem.

Foundations certainly have a role in this area, because they can jump on new ideas early, seed promising lines of investigation, and provide "venture capital" for the development of new technologies and instrumentation. The flip side of this development, however, is providing access to equipment to all qualified researchers. The panelists agreed that lack of ready access to the most useful mix or array of scientific instrumentation is a real barrier to productivity. As Dr. Cassman noted, "It's just too hard for people in many different disciplines to get access to the kinds of instruments that they need on an almost daily basis." This is a key reason institutions are beginning to pool their resources to establish shared core facilities equipped with state-of-the-art instrumentation.

ENCOURAGING SUCCESSFUL ACCIDENTS

The history of science is written in unexpected discoveries and in the "ah-ha" moments of creative insight. In 1883 Sidney Ringer's laboratory ran out of distilled water only to find that river water provided the calcium needed to enable heart muscles to beat outside the body. Similarly, Charles Townes' invention of the maser, which later led to the laser, occurred after he took a walk in Franklin Park. He was wrestling with the apparent limitations imposed by the Second Law of Thermodynamics. During his walk, however, he realized, in a flash of insight, that he need not assume thermal equilibrium. Dr. Will Happer spoke about the importance of the types of environments that make "happy accidents" possible, and the role private foundations like the W. M. Keck Foundation can serve in creating them. "I don't know quite how you do that," he mused, "but I think the best way is to support bright people, and then when an accident happens these scientists will recognize it and something good will come of it."

Dr. Cassman agreed about the value of encouraging accidents. "What is necessary," he stated, "is to ensure that money is given for an idea, which can then turn into another idea or a different train of thought, without anybody seeing that as a penalty."

NEXT STEPS

Listening to these discussions, it seemed to us that there may be some incompatibility between the current system of science administration and the way science will need to be done to address the big issues facing us in the future. To meet these challenges we need to invent new paradigms that govern not only the scientific method, but also the people doing the science and the processes by which they function and interact. The essays that follow, by Drs. Happer and Pardes, suggest possible avenues for further thought and investigation.

DR. WILLIAM HAPPER

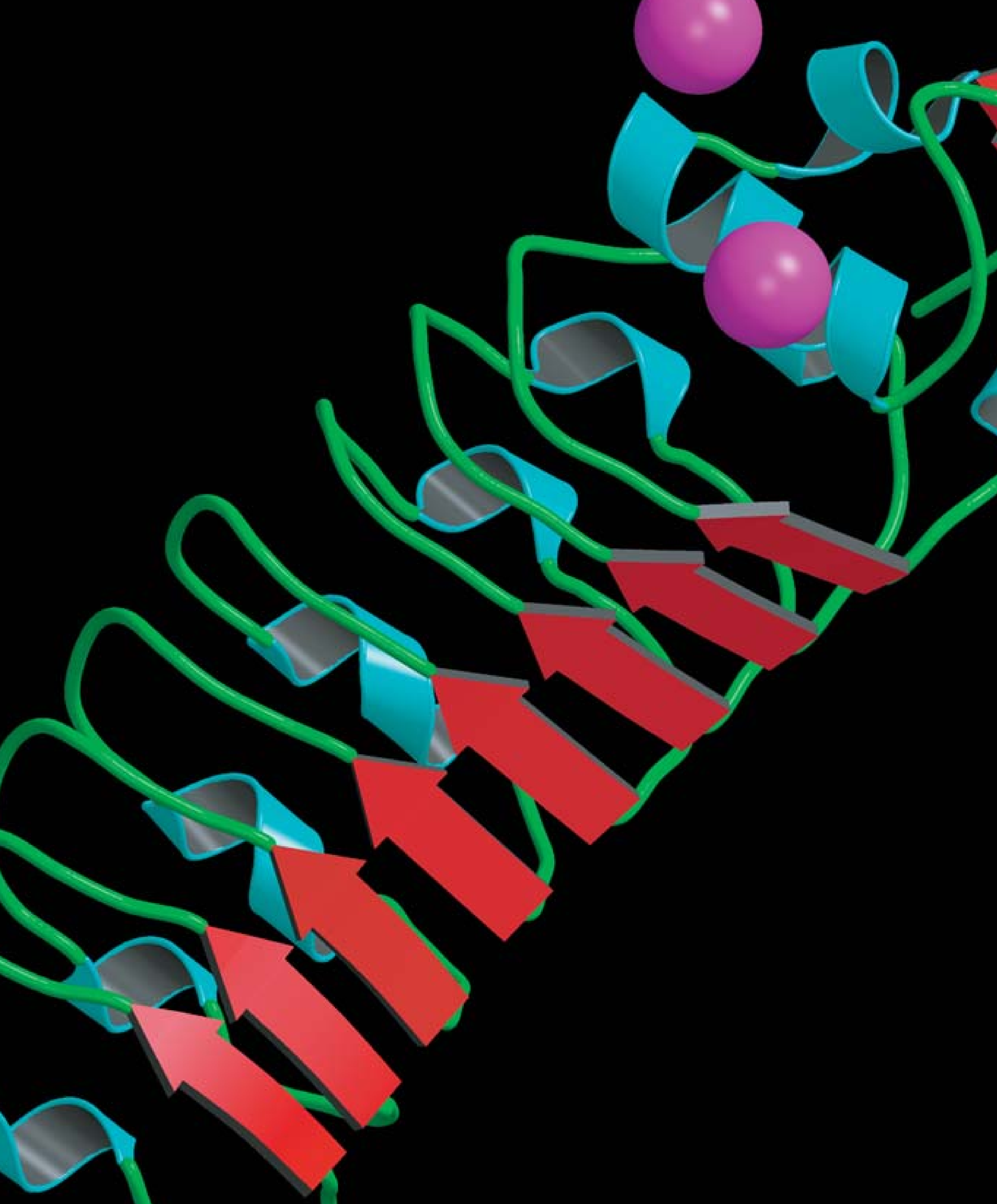
DR. MARVIN CASSMAN

"THERE ARE A HOST OF PROBLEMS THAT WE CAN SOLVE TODAY, AND THE REASON WE DON'T SOLVE THEM IS BECAUSE THE RIGHT PEOPLE AREN'T TALKING TO EACH OTHER."

DR. EVELYN HU

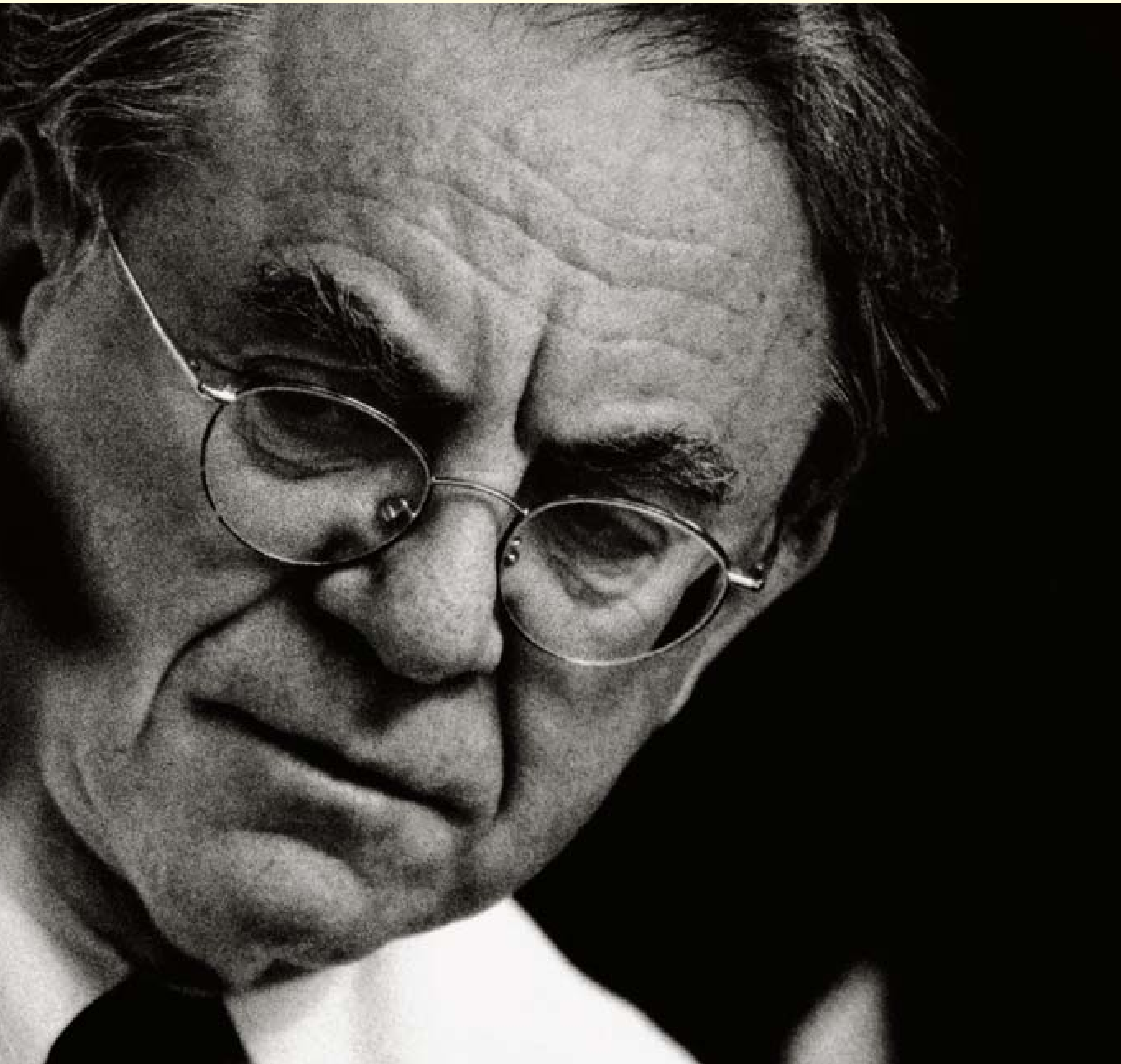
FACILITATING DISCOVERY

Dr. Partho Ghosh, an assistant professor in the Department of Chemistry and Biochemistry at the University of California at San Diego, is a member of the first class of W. M. Keck Foundation Distinguished Young Scholars in Medical Research. This program is just one of a number of ways in which the Foundation attempts to support the human element in the science process. Dr. Ghosh's figure on the following page shows the molecular structure of InlB, a protein found on the food-borne bacteria *Listeria monocytogenes*. InlB interacts with the normal human cell signaling pathway and is taken into the cell. Once inside, it is protected from parts of the host's immune response, and can proliferate, infecting other organs in the host's body. This protein's structure helps illuminate a process of host cell invasion that is common to numerous infectious microbes, and may lead to new ways to design strategies to block infections before they start.



"... IT IS IMPORTANT TO BRING THE BEST AND MOST CREATIVE MINDS TO SCIENCE IN ORDER TO CONTINUE TO EXPLOIT THE FULL POTENTIAL OF WHAT SCIENCE PROMISES."

DR. HERB PARDES, *President and Chief Executive Officer, New York-Presbyterian Hospital*



WHAT IS THE SINGLE MOST IMPORTANT INGREDIENT IN A SUCCESSFUL SCIENTIFIC ENTERPRISE? IT IS THE PEOPLE THEMSELVES. PEOPLE CONCEIVE NEW IDEAS, METHODS, AND QUESTIONS, AND PEOPLE PERFORM THE PAINSTAKING WORK REQUIRED TO INVESTIGATE THEM.

THE W. M. KECK FOUNDATION STAFF

THE BEST AND BRIGHTEST IN SCIENCE

BY DR. HERB PARDES

Science and technology are critical to the health and welfare of our people, the progress of our nation and the strength of our economy. Science has allowed us to expand our energy sources, explore space, develop better medicines, increase longevity, enrich our pleasures, enhance our success in agriculture, industry and a host of other human enterprises and dramatically expand our rich diversity of consumer products.

Given that proposition, it is important to bring the best and most creative minds to science in order to continue to exploit the full potential of what science promises. How to attract such talent requires careful thought and attention.

The excitement of a field is an important determinant of its attractiveness. That attractiveness can vary from time to time. When business captures the public imagination, as has occurred recently, young people in considerable numbers go into the field. The excitement of space exploration drew many into related sciences. Throughout this century, various fields of science have enjoyed peaks and valleys in their level of interest that has, to some degree, been influenced by this sense of excitement.

Also influencing professional choices are the perceived national priorities. What the leadership or the dominant culture is saying about the important disciplines and areas of work has some impact on people's choices. Thus, when the nation became excited about the Peace Corps, many applied and served around the world. At one point in medicine, primary care became of great interest; the national statement of priority in that regard had influence on the career choice of many physicians.

Young people also respond to the opportunity to make a difference. In the face of disasters around the globe, for example, many have volunteered to go to faraway places in order to help. The feeling that their contribution would be of consequence was important in this decision.

Many have chosen fields that in some way related to their own family or personal experience. They cared enough about a particular problem or illness to put themselves into the middle of attempting to solve the problem.

These factors are clearly interrelated. Much of the excitement to which I referred comes from the conviction that a person can make a difference. This in turn relates to the perception of models who seem admired by the society and who receive the indications of a social valuing process. Various disciplines have enjoyed this kind of appreciation by society–newscasters, entertainers, sports heroes, and even on occasion, scientists. As an example of the latter, readers may recall Albert Einstein's recent selection as person of the century by *Time Magazine*.

One must also recognize the link between models and mentors. Someone established in the field and who is admired attracts protégés. Having such a model who can also nurture, function as a guide, sage, and supporter is particularly important

"WE NEED SPECIALIZED TEACHERS IN ELEMENTARY SCHOOLS DOING EXPERIMENTS WITH STUDENTS, TWEAKING THEIR CURIOSITY AND SHOWING THEM HOW TO SOLVE PROBLEMS."

DR. HERB PARDES

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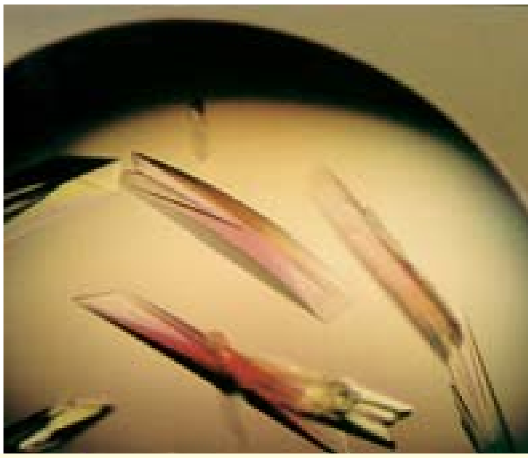
CRYSTALS OF A SEGMENT OF InlB



in fostering the science interest and career success of a young aspirant. This is connected in turn to the quality of science teachers and science teaching a young person experiences in his or her schooling.

Models and mentors must be complemented by concrete opportunities and support. The availability of fellowships, startup support, and opportunities to work in quality laboratories, along with awareness of, and contact with, established scientists who are doing well and are well supported, show that successful career paths are possible. These represent the tangible reassurances prospective scientists seek.

These factors: excitement, national or community values, the perception that the field makes a difference, models, mentors, and concrete support all contribute by providing a context in which the individual with her or his unique personal talent and intellect, and family culture and models, which served as their earliest imprinting factors, converge to create a set towards science. This predilection mixes with these contextual factors to determine an individual's course in or out of science.

What can a concerned leader or concerned institution do to enhance the likelihood that the best and the brightest will choose and succeed in a science career? I would suggest the following:

1. Strengthen the caliber of teachers and quality of science teaching throughout the educational system. We need specialized science teachers in elementary schools doing experiments with students, tweaking their curiosity and showing them how to solve problems. Experiences with the excitement of science are particularly powerful when they occur for young people. Also, as Dr. William Sanders of the University of Tennessee has shown, "teacher effectiveness is ten to twenty times as significant" as the effects of other variables influencing student achievement.
2. Support programs, which link school science teachers to outstanding scientists and their labs in order to keep the teaching of science in the early years fresh and modern in its approach. For example, Columbia University's Summer Research Program for secondary school science teachers provides opportunities for New York City teachers to do

research in the laboratories of Columbia faculty each summer. Students of teachers who participate in the program have shown an improvement in both interest and achievement in their science studies.

3. Provide valued commendations and scholarships to young people who complete quality science projects.
4. Provide concrete and generous financial support for science mentors for salary, materials and personnel. Reward those who mentor students in their lab and who reach out to students in elementary, secondary and undergraduate colleges, especially in less well-funded school districts.
5. Showcase successful scientists and their work in widely viewed media events. For example, New York-Presbyterian Hospital and Columbia and Cornell Medical Schools sponsor a program of science for the general public at the American Museum of Natural History.
6. Secure the help of societal leaders from the president and governors to business and media leaders, amongst others, to publicize their valuing of science and scientists.
7. Promote a rich menu of scholarships, fellowships, startup money, and pilot projects by funding entities that are facilitating and applicant-friendly. Create grant programs of small amounts to fund projects for young people with increasingly large funding levels as they advance. Show them opportunity. Increase salaries and benefits for postdoctoral scientists to livable levels.
8. Provide support for science education for the general community so that those not directly involved in science can still understand its value. This helps produce a fostering attitude from these others whose opinions or attitudes may be important to budding scientists and to the general climate of support for science.

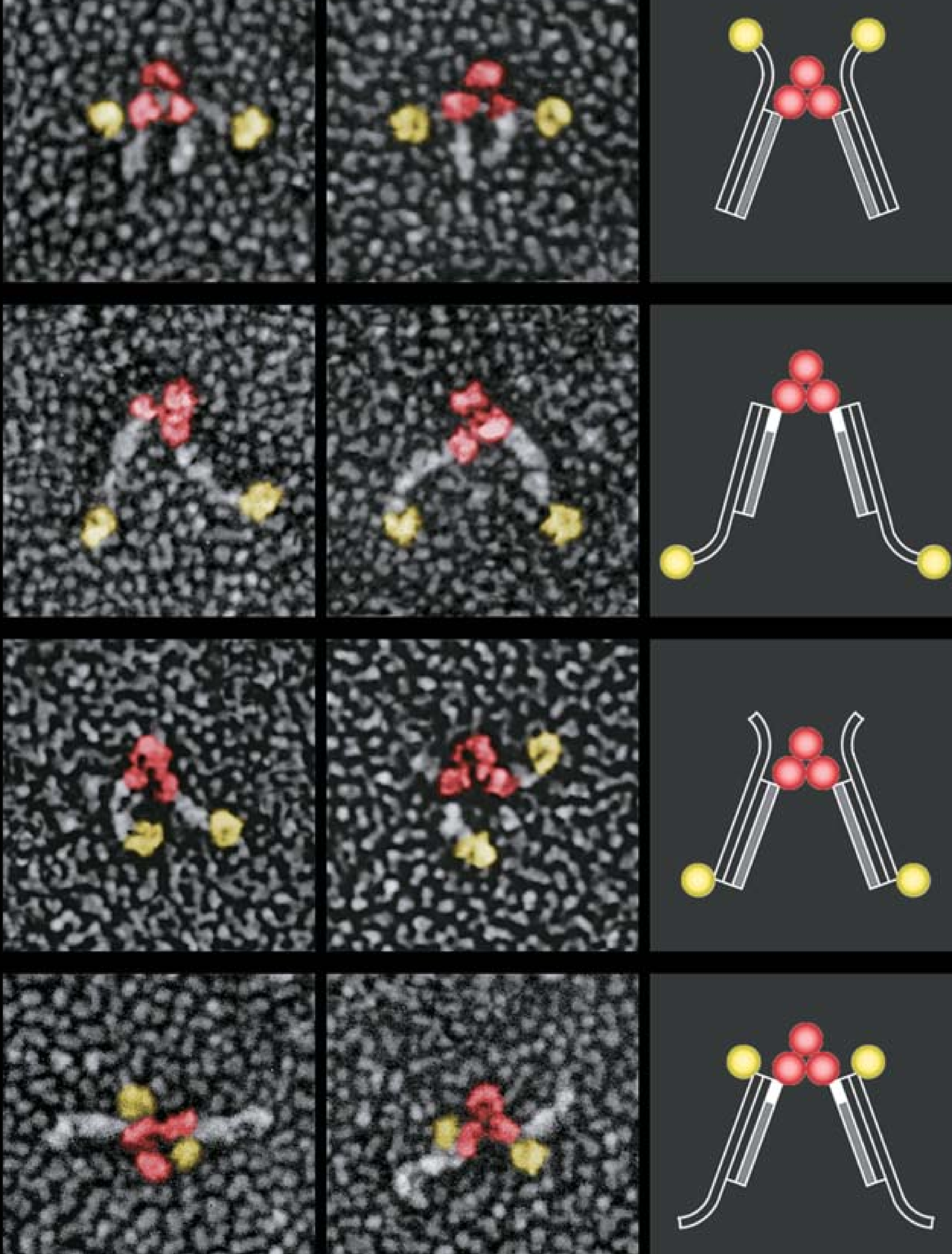
Of concern too is recruitment of minority students. The presence of model minority science leaders can have an important impact on the interest of young people. The sense of familiarity that derives from contact with like individuals already in the field, who serve as models and mentors, cannot be overstated. And, if some emerge from particularly financially needy families, the opportunity for debt relief, enhanced living support, and generous loans has to be considered.

One further population that is of particular concern to the future of model research is the clinical investigator. There is a decline in the number of physicians applying for NIH support. The NIH has implemented a number of steps to address this problem. Augmenting these with efforts by foundations would help because the supplementary money that used to be available from clinical revenues, academic medical centers and institutional monies is increasingly scarce. Also, medical school debt relief has still not been secured. Those entering clinical research are often burdened with $100,000 or more of debt from their professional training.

In the end, any one person's professional choice is highly individually determined. Some people are highly focused and have been driven to do science from childhood. They constitute a special, and likely very promising group. But not all scientists are like that. Given the preponderance of factors beyond individual makeup, some focused efforts will be necessary to attract young people to science and meet the national need for an outstanding scientific cadre.

ENCOURAGING ACCIDENTS

Dr. Phyllis Hanson, assistant professor in the Department of Cell Biology and Physiology at the Washington University in St. Louis School of Medicine, is another W. M. Keck Foundation Distinguished Young Scholar. Dr. Hanson studies the membrane fusion events by which cells release signalling molecules and take in nutrients. Cell membranes and the proteins they contain have been particularly difficult to study using standard structural techniques because these require soluble proteins. The series on the following page of deep-etch electron micrographs, magnified 300,000 times, of membrane protein complexes (grey) with tagging proteins (colored), has helped to elucidate the mechanism used by cells to fuse membranes. Dr. Hanson's investigations on SNARE complexes revealed the shape and parallel orientation of v- and t-SNAREs within such complexes, and suggested a simple and general mechanism for membrane fusion quite different from the then prevailing theories. This mechanism is now generally accepted, and explains some of the complexity in cell membrane function.



THE HISTORY OF SCIENCE IS WRITTEN IN UNEXPECTED DISCOVERIES AND IN THE 'AH-HA' MOMENTS OF CREATIVE INSIGHT. ENCOURAGING THE EXPLORATIONS THAT WILL EVENTUALLY LEAD TO THESE DISCOVERIES MAY REQUIRE THE INVENTION OF PARADIGMS THAT GOVERN HOW PEOPLE DO SCIENCE AND THE PROCESSES BY WHICH THEY FUNCTION AND INTERACT.

THE W. M. KECK FOUNDATION STAFF

ENCOURAGING HAPPY ACCIDENTS IN SCIENCE

BY DR. WILLIAM HAPPER

History shows that major advances in science have often come from accidents. For example, Konrad Roentgen discovered x-rays because he followed up his observations of an unusual glow from fluorescent materials situated – by accident – near cathode ray tubes. Alexander Fleming's curiosity about the destruction of bacterial cultures by contaminating molds led to the discovery of penicillin. Jocelyn Bell's persistence in tracking down interference in a new radio telescope led to the discovery of pulsars.

Enlightened science policy can make scientific accidents more likely. Successful accidents happen to talented people, so it is essential that society encourage new generations of our most gifted young men and women to undertake

"ENLIGHTENED SCIENCE POLICY CAN MAKE SCIENTIFIC ACCIDENTS MORE LIKELY."

DR. WILLIAM HAPPER, *Eugene Higgens Professor of Physics and Chair of the University Research Board at Princeton University*

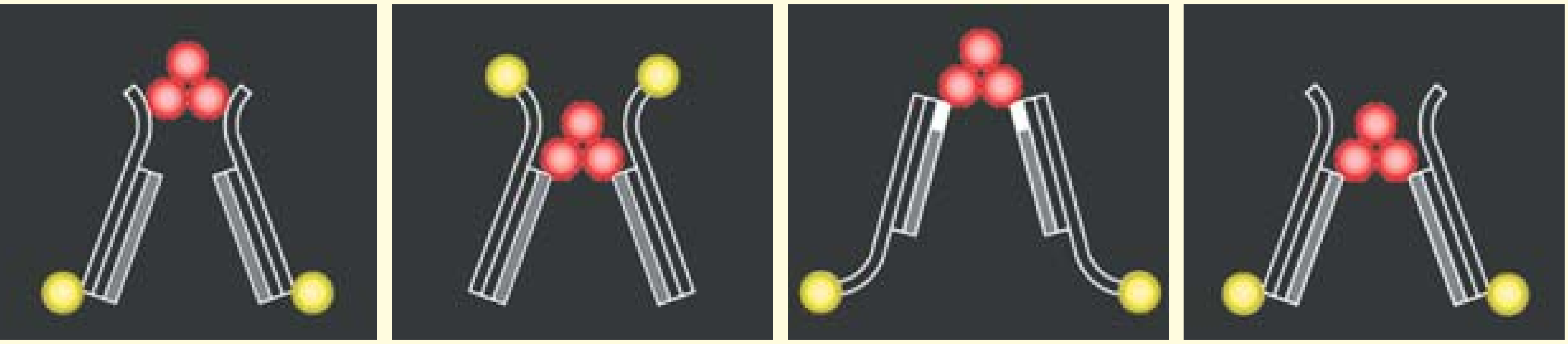
scientific careers. In some scientific fields, would-be researchers face a daunting future, with long years of training and uncertain prospects for permanent employment. Reasonable scientific career prospects will encourage young people, who are the only source of future accidents, to stay in science.

Accidents often occur when new experimental tools become available. The new tools may or may not be expensive, but they have to offer new opportunities for observation. For example, the vacuum pumps needed to evacuate cathode ray tubes, and the induction coils for generating pulses of high voltage were relatively new at end of the 19th century, and Roentgen could afford them on a modest research budget. Jocelyn Bell could not have discovered pulsars without an innovative radio telescope. The cost of the radio telescope was a bit greater, in real terms, than Roentgen's equipment, but it was much less costly than an advanced new optical telescope. The discovery of the J/\Psi particle, the first clear manifestation of charmed quarks, would not have been possible without particle accelerators and detectors costing many millions of dollars. But accidental discoveries can occur with very inexpensive and seemingly old-fashioned equipment – for example Fleming's bacterial culture plates.

Successful accidents happen to people who have the opportunity to postpone work on the original goal of their research and follow promising leads. Even if the the funding source permits digressions, a researcher needs good judgement to decide when to make a major detour from the original research itinerary. For every accident that changes the course of scientific history, there are a hundred "dirt effects" that lead nowhere.

Substantial additional effort is needed to tell whether a chance observation is a dirt effect or the first hint of an important breakthrough. This may be why an unusual number of accidents are successfully exploited by young people who are not yet burdened by many of the distracting obligations of older researchers.

TERNARY SNARE COMPLEXES



DR. WILLIAM HAPPER

"SUCCESSFUL ACCIDENTS HAPPEN TO PEOPLE WHO HAVE THE OPPORTUNITY TO POSTPONE WORK ON THE ORIGINAL GOAL OF THEIR RESEARCH AND FOLLOW PROMISING LEADS."

DR. WILLIAM HAPPER

Along with innovative research equipment, innate talent, and determination, time is needed to exploit accidental discoveries.

To gain recognition in society, successful accidents usually require further development. For example, penicillin would have remained a laboratory curiosity without the determination of Howard Florey and Ernst Chain to make penicillin useful for treating human diseases. The additional work needed to fully exploit accidents comes more quickly and surely if the author of the accidental discovery is already well-known, is from a well-known institution, or has a well-known sponsor.

Entire subfields of research can become important by accident. To cite one example, basic research on the spectroscopy of rare-earth and transition-metal ions in crystals seemed to be a backwater until it was discovered that many of these same crystals made spectacularly useful lasers. Researchers who had studied the physics and chemistry of such crystals in relative obscurity were suddenly harassed by eager laser builders from government and industry.

Initiatives in fashionable research areas can be useful if they do not unbalance the research portfolio. But since political support is needed for research initiatives, the goals of the initiatives are often unrealistic. A few centuries ago, a common research initiative was funding of alchemists to make gold. Some good came of this, and a slow accumulation of accidents – for example, the discovery of the element phosphorous (an accident) – eventually led to modern chemistry. However, initiatives, especially politically driven ones like the genetics of Lysenko in the Soviet Union, can be a waste of money or worse.

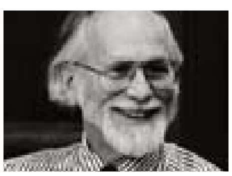
In science as in other areas of human activities the words of Psalm 118 often come true, "The stone that the builders rejected has become the chief cornerstone." It is important to support research in as many fields as we can afford – and to be sure that the results are published and accessible to others. Experience shows that a small fraction of these results will turn out to be cornerstones, but it is not possible to choose cornerstones for edifices we cannot foresee.

CONCLUSION

From the Foundation's point of view, the roundtables were a great success. As onlookers, we were mesmerized by the ideas presented by the participants. Some exchanges were profound, some humorous, and all were illuminating. What we heard will surely help guide the Foundation's directors and staff as we evaluate new and promising directions and priorities for future grant-making. We hope it will be useful to others as well.

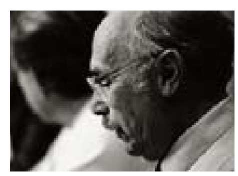
Ultimately, as Dr. Happer noted so eloquently, many of the answers to our questions will come from those "happy accidents" that spring from the alchemy of combining the researchers' bold thinking and hard work, with ample and intelligent investment by private foundations, governmental funding agencies, universities, and private research institutes. We are excited to explore the possibilities illuminated by these roundtables in the years to come.

W. M. KECK FOUNDATION ROUNDTABLES ON THE FUTURE OF SCIENCE PARTICIPANT BIOGRAPHIES



DR. J. MICHAEL BISHOP

Dr. Bishop received his M.D. from Harvard University. In 1998, he was appointed Chancellor of the University of California, San Francisco, where he is also University Professor in the Department of Microbiology and Immunology, and Director of the G.W. Hooper Research Foundation. He is a member of the Board of Trustees at the Salk Institute, and the Board of Overseers for Harvard, and chairs the National Cancer Advisory Board for the National Cancer Institute. In 1989, Dr. Bishop received the Nobel Prize in Physiology or Medicine along with Harold Varmus for their discovery that normal cells contain genes capable of becoming cancer genes. His memberships include the National Academy of Sciences, the American Academy of Arts and Science, and the Institute of Medicine. Dr. Bishop is a Fellow of the American Association for the Advancement of Science.



DR. MARVIN CASSMAN

Dr. Cassman received his B.A., B.S. and M.A. at the University of Chicago, and his Ph.D. at the Albert Einstein School of Medicine. He is currently the Director of the National Institute of General Medical Sciences of the NIH, which he joined in 1975. He has also served in the White House as Senior Policy Analyst in the Office of Science and Technology Policy in the Executive Office of the President, and was a staff member on the House Subcommittee on Science and Technology. Dr. Cassman has received the U.S. Public Health Service's Senior Executive Service Award, and a Presidential Meritorious Award.

DR. GERALD EDELMAN

Dr. Edelman received his B.S. at Ursinus College, his M.D. at the University of Pennsylvania, and his Ph.D. at Rockefeller University. He is currently Director of The Neurosciences Institute and President of The Neurosciences Research Foundation. Separately, he is Professor and Chairman of the Department of Neurobiology at the Scripps Research Institute. Dr. Edelman has made significant research contributions in biophysics, protein chemistry, immunology, cell biology, and neurobiology. His early studies on the structure and diversity of antibodies led to the Nobel Prize for Physiology or Medicine in 1972. He is a member of the National Academy of Sciences and the American Philosophical Society, as well as several foreign societies.

DR. THOMAS EVERHART

Dr. Everhart received his A.B. in Physics at Harvard, his M.Sc. in Applied Physics at the University of California at Los Angeles, and his Ph.D. in Engineering from Clare College at Cambridge University. He was Professor and Chairman of the Department of Electrical Engineering and Computer Science at the University of California at Berkeley, and Dean of the College of Engineering at Cornell University. He served as Chancellor of the University of Illinois at Urbana-Champaign and as President of Caltech, where he is now President Emeritus. He is a Fellow of the Institute of Electrical and Electronics Engineers, the American Association for the Advancement of Science, and the American Academy of Arts and Sciences. He is also a member and councilor of the National Academy of Engineering and is a foreign member of the Royal Academy of Engineering. He is currently Senior Scientific Advisor to the W. M. Keck Foundation, a member of the Caltech Board of Trustees, and the Harvard Board of Overseers.

DR. WILLIAM HAPPER

Dr. Happer received his B.S. in Physics at the University of North Carolina, and his Ph.D. at Princeton. He joined Princeton in 1980, where he is currently the Eugene Higgens Professor of Physics and Chair of the University Research Board. In 1991, he was appointed Director of Energy Research in the Department of Energy by President Bush, where he served until 1993. He has also served on the faculty of Columbia University and is a trustee of the MITRE Corporation and the Richard Lounsbery Foundation. He is co-founder of Magnetic Imaging Technologies, Inc., which specializes in the use of laser polarized noble gases for magnetic resonance imaging. He is a member of JASON, the American Academy of Arts and Sciences, the National Academy of Sciences, and the American Philosophical Society.

DR. LELAND HARTWELL

Dr. Hartwell received his B.S. from Caltech, and his Ph.D. from MIT. He has been a Professor at both the University of California at Irvine and the University of Washington. Dr. Hartwell is currently President and Director of the Fred Hutchinson Cancer Research Center in Seattle, Washington. He has served as President of the Genetics Society of America, on the National Advisory General Medical Sciences Council, and the NCI Cancer Genetics Working Group. He has received several awards, including the American Cancer Society Medal of Honor, the Albert Lasker Basic Medical Research Award, Columbia University's Horwitz Award, Gairdner Foundation International Award, and the General Motors Sloan Award. His memberships include the National Academy of Sciences, and the American Academy of Arts and Sciences.

DR. EVELYN HU

Dr. Hu received her B.A. in Physics from Barnard College, and her M.A. and Ph.D. in Physics from Columbia. She has been a Professor of Electrical and Computer Engineering at University of California at Santa Barbara since 1984, and currently serves as Director of QUEST, an NSF-funded Science and Technology Center. She is also Director of the UCSB node of the NSF-sponsored National Nanofabrication Users Network. She has previously held the positions of Chair of the Department of Electrical and Computer Engineering and Associate Director of the NSF's Center for Robotic Systems in Microelectronics, and was a Member of Technical Staff at Bell Laboratories. Dr. Hu is a Fellow of the Institute of Electrical and Electronics Engineers, the American Physical Society, and the American Association for the Advancement of Science.

DR. NOEL MACDONALD

Dr. MacDonald received his Ph.D. in electrical engineering at the University of California at Berkeley. He spent fifteen years in industry at Rockwell International Science Center, Physical Electronics Industries, and the Perkin Elmer Corporation. He was the Acheson/Laibe Professor in the School of Electrical Engineering at Cornell University and has served as Director of Cornell's Nanofabrication Facility and the National Nanofabrication Users Network. Before taking his current position as Fred Kavli Chair in MicroElectroMechanical Systems (MEMS) and Professor of the Departments of Mechanical and Environmental Engineering and Materials at the University of California, Santa Barbara, he was Director of the Microsystems Technology Office at the Defense Advanced Research Projects Agency. His awards include the 1975 Young Engineer of the Year Award and the Distinguished Alumni Award, Electrical Engineering, University of California, Berkeley. He is a member of the National Academy of Engineering and a Fellow of the Institute of Electrical and Electronics Engineers.

DR. CLAIRE MAX

Dr. Max received her Ph.D. in Astrophysical Sciences at Princeton. She was a postdoctoral fellow in Physics at University of California at Berkeley, and subsequently joined the Lawrence Livermore National Laboratory where she is Director of University Relations. She is leader of the Laboratory's Laser Guide Star Project. Her research interests have included laser-plasma interactions, astrophysical plasmas, and most recently, adaptive optics and laser guide stars. She has served on several national committees, including the National Academy of Sciences' Committee on International Security and Arms Control, the National Research Council's Commission on the Physical Sciences, Mathematics, and Applications, and JASON. Dr. Max is a Fellow of the American Physical Society and the American Association for the Advancement of Science.

DR. HERBERT PARDES

Dr. Pardes received his B.S. from Rutgers University and his M.D. from the State University of New York. He was Vice President for Health Sciences and Dean of the Faculty of Medicine at the College of Physicians & Surgeons of Columbia University before becoming the newly appointed President and CEO of New York-Presbyterian Hospital. He has served as Director of the National Institute of Mental Health and was U.S. Assistant Surgeon General during the Carter and Reagan Administrations. He also served as President of the American Psychiatric Association and Chairman of the Association of American Medical Colleges, the AAMC's Council of Deans, and the New York Association of Medical Schools. He is a member of the Institute of Medicine and has received the Sarnat International Prize in Mental Health and the U.S. Army Commendation Medal.

DR. DINSHAW PATEL

Dr. Patel received his B.S. from the University of Bombay, India, his M.S. from Caltech, and his Ph.D. in Chemistry from New York University. He was a member of Technical Staff at the Bell Laboratories, and Professor of Biochemistry and Molecular Biophysics at the College of Physicians and Surgeons of Columbia University, before taking his current appointment as Abby Rockefeller Mauzé Chair in Experimental Therapeutics in the Cellular Biochemistry and Biophysics Program at the Memorial Sloan-Kettering Cancer Center. Dr. Patel has served on the Structural Biology Scientific Review and Medical Advisory Boards of the Howard Hughes Medical Institute. He has received the AT&T Bell Laboratories Distinguished Technical Staff Award, the New York University's Distinguished Alumnus Award, and has been past President of the Harvey Society.

DR. PETER SCHULTZ

Dr. Schultz received his B.S. in Chemistry and his Ph.D. in Organic Chemistry at Caltech. In 1985 he joined the faculty at the University of California at Berkeley, where he was a Professor in the Department of Chemistry, a Principal Investigator at the Lawrence Berkeley Laboratory, and Howard Hughes Medical Institute Investigator. He is currently a Professor at the Scripps Research Institute and Director of the Genomics Institute of the Novartis Research Foundation. Dr. Schultz has established a research program which spans the disciplines of organic chemistry, molecular biology and immunology. His memberships include the National Academy of Sciences and Institute of Medicine. He has received several recent awards, including the Wolf Prize in Chemistry.

DR. DAVID SCHWARTZ

Dr. Schwartz received his B.A. from Hampshire College, and his Ph.D. from Columbia University. He worked as a staff associate at the Carnegie Institution of Washington's Department of Embryology, and has been a Lucille P. Markey Scholar from 1988-1996. He was made a Presidential Young Investigator by the National Science Foundation and was awarded a Beckman Young Investigatorship. He holds a joint position with the Department of Chemistry in the Faculty of Arts and Sciences, the Department of Computer Science of the Courant Institute of Mathematical Sciences, and the Department of Biochemistry at New York University School of Medicine. In 1999, Dr. Schwartz joined the faculty of the University of Wisconsin, Madison, as Professor of Chemistry and Genetics.

DR. EDWARD STOLPER

Dr. Stolper received his Ph.D. from Harvard University. He joined the California Institute of Technology faculty in 1979, where he is currently the Chairman of the Division of Geological and Planetary Sciences and the William E. Leonhard Professor of Geology. He is recognized for illuminating the chemical differentiation of the Earth through creative experimental and theoretical studies of the density relations between rock melts and crystals at great depth in the Earth and the role of chemical speciation of dissolved water and carbon dioxide in determining the properties of magmas. Dr. Stolper is a member of the National Academy of Sciences.

DR. IVAN SUTHERLAND

Dr. Sutherland received his B.S. from Carnegie Tech, his M.S. from Caltech, and his Ph.D. from MIT, all in Electrical Engineering. After serving as Director of the Information Processing Techniques Office at the Defense Advanced Research Projects Agency, he was Gordon McKay Associate Professor of Electrical Engineering at Harvard. He then co-founded the Evans and Sutherland Computer Corporation and served as Vice President and Chief Scientist. At Caltech, where he was Professor of Computer Science, he helped initiate the Silicon Structures Project. Dr. Sutherland is currently Vice President and Fellow of Sun Microsystems. His memberships include the National Academy of Sciences and the National Academy of Engineering. His awards include the Association of Computing Machinery's Turing Award, the Smithsonian Price Waterhouse Information Technology Leadership Award for Lifetime Achievement, and the IEEE Von Neumann Award.

DR. KIP THORNE

Dr. Thorne received his B.S. at the California Institute of Technology, and his Ph.D. from Princeton. He joined Caltech in 1967 where is currently Feynman Professor of Theoretical Physics. He was co-founder of the Laser Interferometer Gravitational Wave Observatory Project, and is a member of the American Academy of Arts and Sciences and the National Academy of Sciences. He has served on the International Committee on General Relativity and Gravitation, the Committee on US-USSR Cooperation in Physics, and the National Academy of Science's Space Science Board. He has been a Woodrow Wilson Fellow, a Danforth Foundation Fellow, a Fulbright Fellow, and a Guggenheim Fellow. Dr. Thorne's awards include the Lilienfeld Prize of the American Physical Society, and the American Institute of Physics Science Writing Award in Physics and Astronomy.

DR. SHIRLEY TILGHMAN

Dr. Tilghman received her B.S. at Queen's University in Canada, and her Ph.D. in Biochemistry at Temple University. After postdoctoral work with Philip Leder at the NIH, she held positions at Temple University and the Institute for Cancer Research, before joining the faculty of Princeton. She is currently an investigator of the Howard Hughes Medical Institute, and Howard A. Prior Professor of Life Sciences in the Department of Molecular Biology. In 1998, she was named founding director of the Institute for Integrative Genomics, Princeton's planned interdisciplinary center which will focus on integration and complexity in biology. Dr. Tilghman is a Fellow of the Royal Society of London and Member of the National Academy of Sciences and the Institute of Medicine.

DR. EUGENE WONG

Dr. Wong received his B.S. and Ph.D. in Electrical Engineering at Princeton. Since 1998 he has held the position of Assistant Director for Engineering for the National Science Foundation, and has been the Chief Scientist and member of the Board of Directors of Versata Inc. He was a faculty member at the University of California at Berkeley for thirty-two years, and during the Bush Administration served as Associate Director of the Office of Science and Technology Policy. He later held the position of Vice President for R&D at the University of Science and Technology in Hong Kong. Dr. Wong is a member of the Association for Computing Machinery, a Fellow of the Institute of Electrical and Electronics Engineers, and a Member and Councilor of the National Academy of Engineering.

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