BY KIM RIBBINK

A World

PAUL HERRLING, PH.D.,

appreciates the intricacy and multidimensionality of life, whether he is conducting experiments in the lab, overseeing corporate decisions in the boardroom, or collecting and cataloguing antique science books.

HE EXTENDS THIS DEEPLY CONSIDERED WORLD VIEW TO THE ISSUE OF MEDICINE AND THE DEVELOPING WORLD WHILE CREATING AN ENVIRONMENT THAT STRIVES FOR COLLABORATION AND DIVERSITY OF THOUGHT.

From his upbringing in Egypt, through his studies, and into his long and varied career at Novartis, Paul Herrling, Ph.D., has thrived on developing a sense of community and interaction. His efforts at team building and ensuring collaboration have resulted in many successes and opportunities for Novartis and the company's scientists. In his position as head of corporate research at Novartis, he has created a culture that encourages diversity of ideas and input from scientists from all levels of the organization.

"Drug discovery begins with many ideas, but to move a project from the basic science level to the clinic, it's necessary to have multidisciplinary teams, including chemists, molecular biologists, geneticists, physiologists, and pharmacologists who all work together," he says. "Making sure the decision-making process is transparent and allowing ideas to be shared is extremely important. When tough decisions have to be made, such as those that involve killing projects, if the individuals understand the motivation and reasoning behind the decision and appreciate that those decisions are made fairly, they will respect the process and be motivated to become involved in new projects."

As a world leader in pharmaceuticals and consumer health, Novartis works extensively with academic institutions and with partners in the industry to optimize its drug-discovery and development processes. In recent years, Novartis has taken a lead — with significant input from Prof. Herrling — to address the issue of providing access to medicines to patients in the developing world. In addition to several initiatives with the World Health Organization that provide medicine at cost to patients to treat diseases such as leprosy, malaria, and tuberculosis, the company has established three indepen-

VISION

dent corporate research institutes to address unmet medical needs.

As head of corporate research, Prof. Herrling oversees the three institutes: The Genomics Institute of the Novartis Research Foundation (GNF); the Friedrich Miescher Institute for Biomedical Research (FMI); and the Novartis Institute for Tropical Diseases (NITD).

"These institutes bring together special projects that are important to the company," Prof. Herrling says. "While each is related to our mainstream research, it is important that they have some distance from the company to fulfill their missions." (For more information about the foundations, see box on page 50.)

THROUGH THE MICROSCOPE

Raised in Alexandria, Egypt, before moving to Switzerland at the age of 11, the young Paul Herrling was exposed to vastly different cultures, outlooks, and ways of life.

"Both sets of my grandparents left Switzerland in the late 1800s, and my parents met in Egypt," he says.

It was a time when multicultural interaction was a way of life in Alexandria. Most people spoke several languages and socialized with others from many different faiths — Copts, Christians, Muslims, Jews — as well as different nationalities, including Syrians, Lebanese, Greeks, Italians, Swiss, and of course Egyptians.

"The interest in different cultures and interacting with people with different backgrounds is something that has always stayed with me; I really enjoy this multicultural interaction," Prof. Herrling says.

In 1956, when Egypt began to expel European residents following the Suez invasion, he returned with his family to Switzerland, where he attended a boarding school.

It was during his schooling that Prof. Herrling first developed his love of biology. Later, motivated by his professor at Zurich University, Ruediger Wehner, he undertook his thesis on the navigation of ants in North Africa.

"My research focused on finding and identifying the specific receptors in the eye of the ant that are responsible for its navigation behavior, which is the same as the navigation behavior of bees," Prof. Herrling says. "Finding the receptors was very interesting, and the work turned out to be very valuable training."

The multidisciplinary project awakened a strong interest in the nervous system, and Prof. Herrling was eager to find practical applications for his research.

He joined Sandoz as a postdoctoral researcher in 1975 and completed his first postdoctoral degree with a biochemistry group in Basel before doing his second postdoctoral studies at UCLA.

"At UCLA, I studied electrophysiology and combined that with pharmacology methods," he says. "This combination of pharmacological and electrophysiological methods — both *in vitro* and *in vivo* — formed the basis of research at my lab at Sandoz in Basel, which I kept from 1978 until 1992."

During this time, Prof. Herrling drew on the findings of Jeff Watkins of the University of Bristol, which showed that glutamate can serve as a transmitter. Based on these data, Prof. Herrling established an excitatory amino acids project at Sandoz, which led to research in schizophrenia and neurodegeneration.

TRIAL AND ERROR

Drug discovery is a roller coaster of ups and downs and successes and failures. Yet Prof. Herrling believes while the hope is always that a lead will result in a successful drug, the failures offer up important lessons as well.

For example, in the field of excitatory amino acids, Prof. Herrling and his team conducted research into a highly specific brain permeable NMDA receptor antagonist, which was being tested as a treatment for epilepsy.

But during Phase III clinical trials it was revealed that the NMDA antagonist caused hallucinations.

Then the compound appeared to show efficacy as an acute treatment after stroke. But further research with animal models revealed that for the treatment to work, it must take place within two hours of stroke, whereas the majority of patients have strokes overnight and typically arrive in the hospital more than seven hours after the event.

Next, studies were focused on head trauma patients. Even though these patients are typically rushed to the hospital after an accident, because of the need to obtain consent, again, time was not on the researchers' side.

"Because this was an investigational drug, we needed to obtain consent; but since most patients were unconscious, we needed the consent of the family," he says. "By the time consent could be given, about six or seven hours had gone by, and the window for treatment had passed."

Though the research proved disappointing, Prof. Herrling says he learned some valuable lessons and honed his drug-discovery skills.

Despite some setbacks, there has been much to celebrate. Prof. Herrling has been involved with many projects that have resulted in successful drug products, including the development of the antischizophrenic drug clozapine and the cancer treatment Gleevec.

One of the accomplishments of which he is most proud is the group he helped to create many years ago that has been doing some exciting and promising work in the area of Alzheimer's disease.

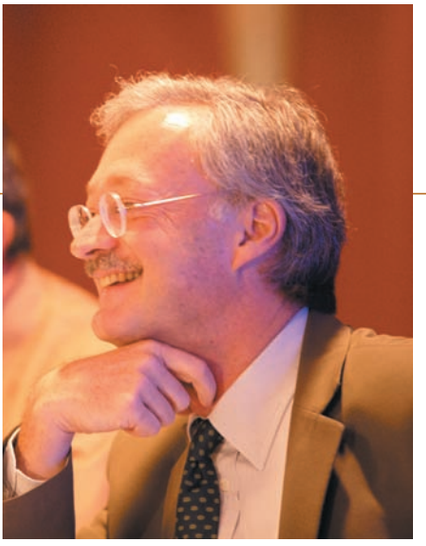
In the early 1990s, Prof. Herrling established a molecular biology group to take advantage of new genetic discoveries.

"We developed one of the first really useful Alzheimer's models — a transgenic mouse that incorporated the human mutations in the APP molecule," he says.

Subsequently, two transgenic mouse lines were generated that expressed human APP751 containing familial Alzheimer's disease mutations in brain neurons. In Alzheimer's disease, plaques develop in areas of the brain related to memory. These plaques consist predominantly of the beta-amyloid protein, but other proteins, such as apoE, are present as well. Beta-amyloid is a protein fragment cleaved from a larger protein called amyloid precursor protein, or APP, during metabolism.

Normally, soluble beta-amyloid protein is catabolized. But in Alzheimer's disease, beta-amyloid protein is formed inside the cell from cleavage of the APP and is then deposited outside the cell.

"The research gave us a model that had significant homology with the human disease," Prof. Herrling says. "Scientists could now prove that the amyloid is not only a side effect of the disease but also show that these



A CHANGING **DRUG-DISCOVERY ENVIRONMENT**

THE FIELD OF DRUG DISCOVERY HAS GROWN AND CHANGED RAPIDLY IN RECENT YEARS. MOLECULAR BIOLOGY AND THE GENOMICS REVOLUTION HAVE CONTRIBUTED VASTLY TO CURRENT KNOWLEDGE AND THE WAY DRUGS ARE DEVELOPED.

While the pharmaceutical industry develops the drugs that help patients, early innovation in terms of principles of science emerges from academia. Over the years, the industry and academia have formed closer relationships to bring those ideas to fruition, says Paul Herrling, Ph.D., head of corporate research at Novartis.

"The biomedical sciences are exploding in terms of knowledge and insight generation; since most of the early work is done in academia, it's extremely important that our discovery scientists closely interact with academia and are exposed to this changing science as it happens," Prof. Herrling says. "Science changes so fast that we have to be participants in the process to understand where it's going."

Prof. Herrling also believes he has a role to play in ensuring that the science in Switzerland remains of the highest caliber.

"I'm on the board of the Swiss Federal School of Technology, which brings me into the areas of science and education policy," he says. "This is very important because the value of our labs is directly linked to the excellence of the universities around us, so continuing to develop this excellence is absolutely essential."

He says the enthusiasm of students makes working in academia a delight.

"It's rewarding to give a lecture or seminar, have a discussion, and interact with young people who ask challenging questions," he says. "That keeps me young."

FOR PROF. HERRLING, THE APPEAL OF DRUG DISCOVERY AND THE BIOLOGICAL SCIENCES IS BOTH DEEPLY CONSIDERED AND VISCERAL.

"The more I got into the biology, the more I became convinced that as a biologist I was in a unique position to understand the world around me," he says. "There are so many everyday things that can be related to biology. This has always been extremely fascinating to me."

Watching the explosive development of biological science has been thrilling, Prof. Herrling says.

"When I started in the industry in 1975, nobody had seen a receptor; a pharmacological receptor was nothing more than a mathematical construct derived from the interaction of tissues with drugs," he says. "Since then, the entire genome has been mapped, and we have the three-dimensional structure of practically all of the receptors that our drugs work on."

Even as science has advanced by leaps and bounds, the industry has been facing a backlash of negative public opinion that has the potential to undermine the work being done.

"For too long we took it for granted that we were saving lives and that our work should be valued," he says. "Now, people mostly see the industry as increasing the costs of medicines; we have not communicated the advances and the contribution we make to society."

He says if this perception gets too strong, regulations and laws will ultimately limit the pharmaceutical industry's potential to innovate.

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A LOOK AT **NOVARTIS' RESEARCH ORGANIZATION**

Pharmaceutical research at Novartis is conducted primarily through the Novartis Institutes for BioMedical Research (NIBR), which is under the leadership of Mark C. Fishman, M.D.

NIBR, which has headquarters in Cambridge, Mass., crosses both geographical and specialty boundaries. Within NIBR are groups of scientists specializing in particular disease areas, such as oncology, diabetes, or arthritis, as well as "platforms" that focus on more fundamental scientific disciplines that apply across a broad spectrum of diseases. The Cambridge headquarters will continue to grow, with a $4 billion investment planned over the next 10 years.

Additionally, the company has created an area known as corporate research, whose mission is to leverage the specific scientific expertise of its three member institutes to address unmet medical needs, with a particular focus on the developing world and neglected diseases.

With a total staff of more than 750 scientists, the institutes are: The Friedrich Miescher Institute for Biomedical Research (FMI) in Basel; The Genomics Institute of the Novartis Research Foundation (GNF) in La Jolla, Calif.; and The Novartis Institute for Tropical Diseases (NITD) in Singapore.

Founded in 1970, the Friedrich Miescher Institute, which is headed by Susan Gasser, is devoted to fundamental biomedical research and employs new technologies to explore basic molecular mechanisms of cells and organisms in health and disease. Research focuses on the fields of epigenetics, growth control, and neurobiology. In addition to basic science, the institute also has about 150 students who are given an opportunity to participate in scientific research at the postgraduate and postdoctoral levels.

"This is a very important partner for pharma research because the institute is exploring fundamental biological principles that can then become projects on the commercial side," says Paul Herrling, Ph.D., head of corporate research at Novartis. "For example, the scientists at FMI worked for many years on kinases before it was taken up by the commercial operations, which showed that kinases can be valuable drug targets. That work eventually led to the development of Gleevec."

GNF, which was founded in 1999, is developing advanced technologies, ranging from cellular genomics and proteomics to combinatorial chemistry and structural biology. The mission of GNF, headed by Peter Schultz, is to exploit these technologies to identify new biological processes and understand the underlying mechanisms involved in human disease.

"GNF was established at the time when introducing high-throughput equipment in the biological labs was becoming more and more important because of the complexity of the biology of disease that was emerging," Prof. Herrling says. "The GNF Institute hired 40 engineers from the car industry; together with a group of biologists, they developed everything from high-throughput crystallization of proteins for structural elucidations, to high-throughput screening of proteins or cellular high-throughput screening, and so on. Having explored new methods, they're now applying that work, doing their own drug discovery, and putting important compounds in our pipeline."

In addition to its internal resources, the institute is located near the Scripps Research Institute and other international researchers in southern California.

A few years ago, Daniel Vasella, M.D., chairman and CEO of Novartis, discussed with Prof. Herrling the issue of access to medicine in the developing world and out of that meeting the NITD was born. The NITD is bringing the ongoing revolution in biomedical science and technology to bear on diseases of the developing world, initially tuberculosis and dengue fever. Alex Matter, M.D., is director of the NITD in Singapore.

TB, which is a bacterial infection caused by Mycobacterium tuberculosis, is a leading cause of death and disease worldwide. Close to 8 million people are infected annually. TB has reached epidemic proportions in part due to immunocompromised patients, with diseases such as HIV/AIDS, residing in endemic areas. Inappropriate use of antibiotics also has led to an increase in drug-resistant strains.

The global prevalence of dengue fever continues to rise and is now endemic in more than 100 countries in Africa, the Americas, and the eastern Mediterranean. The most serious outbreaks are found in southeast Asia and the western Pacific. The World Health Organization (WHO) estimates that 50 million cases occur each year, requiring 500,000 hospitalizations.

Drugs that come out of the NITD's research will be made available at cost to patients in need in the developing world.

"After deciding to establish this institute, we then had to decide where it would be located," Prof. Herrling says. "It was important to put the researchers who are developing the medicines close to patients and their doctors. On the other hand, we couldn't put this institute in the middle of the jungle, because we would need access to scientific talent, political stability, intellectual property laws, animal experimentation laws, and so on. There was a whole list of criteria that needed to be filled."

At the time, Singapore was making concerted efforts to attract drug-discovery sciences from big pharma because the city-state had decided that the biomedical sciences should be a strategic priority.

"The economic development board of Singapore decided that it would support us setting up this institute and contributed to a partnership," Prof. Herrling says. "It's a public/private partnership that is financing some part of the activity we have there.

"The institute opened two years ago, and it's already established itself as one of the important players in the area of access to medicine," Prof. Herrling says. "We've allocated one of our very best drug discoverers to head this institute: Dr. Matter, who discovered Gleevec."

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mutations produce an excessive production of the beta for peptides out of the APP. These experiments were extremely important to show that amyloid plaques are causally related to the disease process. The work produced by this excellent group, which is really pretty well known worldwide, has resulted in an Alzheimer's vaccine, which is soon going to be tested in the clinic."

Though he has been with the company for more than 30 years, Prof. Herrling says he remains excited by the work he is doing.

"Since the time I was a bench scientist, I've always felt I was contributing to building something," he says. "From having my own lab with three or four people, to running the Sandoz Forschungs Institute Bern AG with about 200 people, to overseeing a national and then global research organization, I've been afforded the opportunity to work on many exciting, collaborative projects."

One such project included work with a number of companies to establish the single nucleotide polymorphisms, or SNPs, consortium.

"Several companies came together to finance a genetic map of the single nucleotide polymorphisms and put it in the public domain," Prof. Herrling says. "Novartis also established an intensive collaboration with Celera, where we had access to three genomes — fly, mouse, and human — compared side by side, which was another exciting project to work on."

LIFE IN **RESEARCH**

PAUL HERRLING – RESUME

JANUARY 2003 – PRESENT. Head of Corporate Research, Novartis International AG, Basel, Switzerland

2002 – PRESENT. Full Adjunct Professor, Harold Dorris Neurological Institute, The Scripps Research Institute, La Jolla, Calif.

2001 – PRESENT. Professor for Drug Discovery Science, Philosophisch-Naturwissenschaftliche Fakultaet, University of Basel, Switzerland

JANUARY 1997 – OCTOBER 2002. Head of Research, Novartis Pharma AG, Member of the Novartis Pharma Executive Board

JANUARY 1994 – DECEMBER 1996. Head of Corporate Research, Sandoz Pharma Ltd.; Senior VP, Member of the Board of Management

MAY 1992 – DECEMBER 1993. Head of Preclinical Research Basel, Switzerland, Sandoz Pharma Ltd.; VP, Deputy Member of the Board of Management

JANUARY 1987 – APRIL 1992. Vice Director, Head of Sandoz Research Institute Berne Ltd., Head of Preclinical CNS Research Dept., Sandoz Pharma Ltd., Basel, Switzerland

1985 – 1986. Deputy Head of Preclinical CNS Research Department, Wander Ltd., Berne, Switzerland (as of January 1987 Sandoz Research Institute Berne Ltd., Switzerland)

1983 – 1985. Deputy Head of Preclinical Psychiatry/Neurology, Research Department, Wander Ltd., Berne, Switzerland

JANUARY 1982 - PRESENT Attorney Holder

1981 – 1983. Head of Laboratory, Preclinical Research, Wander Ltd., a Sandoz Res. Unit, Berne, Switzerland

1977 – 1981. Head of Laboratory, Preclinical Research, Sandoz Pharma Ltd., Basel, Switzerland

EDUCATION

1976 – 1977. Postdoctoral Fellow, Prof. N.A. Buchwald, Mental Retardation Research Center, Neuropsychiatric Institute, UCLA, Los Angeles

1975 – 1976. Postdoctoral Fellow, Dr. R. Markstein, Preclinical Research, Sandoz Ltd., Basel, Switzerland

1971 – 1975. Kantonsassistent, Department of Zoology, University of Zürich, Ph.D. Thesis with Prof. R. Wehner

1971. Master of Science, University of Zürich

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Board of the ETH (Swiss Federal Institute of Technology)

Board of Directors of the TB Alliance

Board of Directors of Chiron

A WORLD **VIEW**

The 1996 merger of Ciba and Sandoz, which led to the formation of Novartis brought for Prof. Herrling a new challenge: integrating two large organizations harmoniously so that the scientists could quickly and painlessly return to the job of developing drugs.

As head of global research at the time, Prof. Herrling put in place several key steps that streamlined the integration process. He ensured that the selection process with regard to who would be in charge of various departments was handled early on, thereby shortening the period of uncertainty.

All of this was done openly and with transparency so that it was clear that decisions were based on excellence and not on company politics.

"The result was a team that was a nice mix of individuals representing both organizations," he says.

The next step was to create a forum comprised of the company's most senior research managers to referee projects.

"With a research organization of 2,500 people it's impossible for one person to make evidence-based decisions about the many projects taking place across numerous scientific areas," Prof. Herrling says. "Bringing together a senior management team built a lot of bridges across departments."

Prof. Herrling also eliminated the geographic scientific manager positions and replaced those roles with global heads of various therapeutic categories, such as oncology, central nervous system, immunology, etc.

"This guaranteed that there would be no redundancies in any one field because the category was under the supervision of one person who had a budget with a lot of entrepreneurial freedom in terms of allocating funds," he says.

True to his belief in maintaining transparency, Prof. Herrling also made sure that every scientist on a team was involved in the decision-making process.

"Whenever there was a decision to be made about a project, we would invite all of the team members who had contributed to that project to sit in the meeting," he says. "This inclusiveness accomplished two things. One, we were sure not to make foolish decisions because we ignored some detail or scientific fact that only the project team knew; and two, since the team was part of the referee meeting, they understood why and how decisions were made."

With his vast experience in drug discovery and development, Prof. Herrling, more than most, is sentient to the difficulties that continue to limit access to medicine by those most in need.

"Access to medicine in the developing world is limited by a large number of factors," Prof. Herrling says. "Obviously one factor is cost and the distribution of products to where the patients need them. Other important aspects are education, culture, and literacy. Many of the patients do not know how to use Western-based medicine. But there also is another element: many of the diseases of the developing world, which are affecting millions of people, are not being researched."

As a commercial operation, the pharmaceutical industry needs to invest in areas where it can have a return. Novartis, however, decided it needed to play a role in ensuring access to medicine for the poorest in society.

The company decided to apply some of its leading-edge drug-discovery sciences and technologies to diseases impacting developing countries.

With Prof. Herrling at the helm of corporate research for Novartis, the company established NITD. This group currently is focusing its efforts on dengue fever, which is transmitted to humans through the bites of infected mosquitoes, and tuberculosis.

Though eager to bring relief to developing nations, the company recognizes that change can only be brought about one step at a time and in collaboration with many partners, be they NGOs, foundations such as the Bill and Melinda Gates Foundation, local governments, and organizations within the countries it is working in.

Prof. Herrling also has taken up the torch of scientific ambassadorship, whereby he represents the company as a scientist.

"The public often thinks that companies steal ideas from academia; they have no idea of what drug discovery is or what is involved to take a basic scientific idea and translate that knowledge into a medicine," Prof. Herrling says. "The pharmaceutical industry has not communicated very well to the public the value that it brings; therefore there's a lot of misunderstanding of what it is that we really do.

"I'm also interacting with health and science ministries, particularly in Asia, and organizing small scientific symposia where our scientists interact with scientists from the country we visit and at the same time we involve the science ministry and the health ministry in discussions about what the pharma industry is, what we can do for them, and what they can do for us," Prof. Herrling says.✦

PharmaVOICE welcomes comments about this article. E-mail us at feedback@pharmavoice.com.