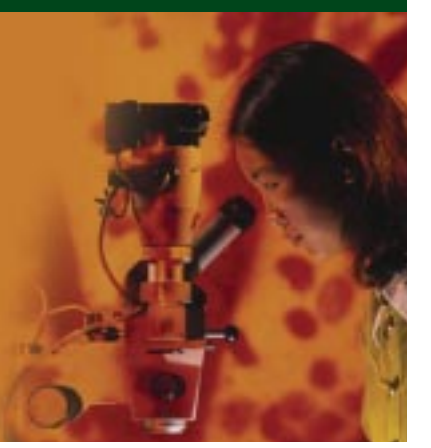
EuroTimes visits the
US National Eye Institute



The National Eye Institute rests in a bucolic setting on the Bethesda Maryland campus of the US National Institutes of Health, just a few miles from Washington DC. While it may be best known for handing out research grants and sponsoring large scale epidemiological and clinical studies such as AREDS and OHTS, it is also a research entity in its own right, performing an array of research from the most basic science to innovative clinical studies.

Paul Sieving MD PhD has been the director of the NEI since 2001. He heads the organisation at a time of tectonic shifts in population demographics, changing research priorities, and renewed attention to ethical research standards. EuroTimes Editor Sean Henahan spoke with Dr Sieving recently to gain some perspective on what's going on behind the walls of NEI.

ET: Our readers probably know very little about NEI. Could you give us a brief summary of what it is and what it does?

Sieving: The NEI is one of 27 components of the National Institutes of Health. We receive $700 million in federal funding per year, which actually makes us one of the smaller institutes at NIH. In house we have approximately 500 people in research and administration. We allocate $550 million of our budget to outside grants to the US and international research communities. The quality of vision science at this time is impressive. This presents a tremendous opportunity for all of science to learn some of the basic lessons of how cells and bodies work by looking at the visual system.

ET: One of your administrative tasks is handing out more than half a billion dollars every year. How do you determine how to distribute the money?

Sieving: In fact, I sign the checks, while the actual decisions to award grants are made by groups of peer scientist reviewers. Essentially we try to fund the projects that have the highest quality. We have a peer review process divided into sections. Our reviewers then determine where the opportunity and quality fit in the placement of grants. Fortunately I don't have to know every last detail of every single grant; that would be impossible. Approximately one third of grant applications eventually receive funding.

ET: You allocate a majority of your budget to extramural researcher projects, but the NEI also conducts basic and clinical research here in Bethesda. How do you make those decisions?

Sieving: All of NIH wrestles with this issue. In general, all NIH institutes allocate about the same proportion for intramural research, 9%-11% of our non-administrative money. Generally what NIH as a whole tries to do in-house is to pick topics that are difficult because they take a long period of time, and one has to assemble a critical mass of people to get something done.

There are some practical considerations. People who are here tend to stay here. Researchers here tend to work in a single area for a long period of time. We don't cover the whole of vision research here on campus. We are interested in specific diseases, and we have specific opportunities with our people.

We have work going on in lens, cataract, development of the eye, cornea, and glaucoma and the trabecular meshwork. We also have one of the best groups in the country looking at visual processing. There are other cases where there is special opportunity that the environment here is well suited for. The NEI also has an interest in translational research, that is, taking laboratory findings and trying to apply those to human disease.

ET: There must be a certain amount of overlap at NIH. How do you avoid conflicts and how are research efforts, not to mention budgets, coordinated among the different institutes?

Sieving: We have opportunities on the NIH campus to meet with the other institute directors. The directors tend to have the broader, big picture view. We recently had a daylong science retreat on the NIH Roadmap to discuss long-term directions in research. The Roadmap is an NIH initiative to build bridges between all of the separate disciplines. For example, the NEI is particularly interested in the eye and the visual system; the National Heart Lung and Blood Institute is interested in heart disease. The systems share the same blood vessels. That means that there are opportunities to have vision scientists and cardiologists talking to each other about issues such as diabetes and how that would affect both the heart and the retina.

There are a lot of common opportunities in science. One of the important stories during the next decade will be how Alzheimer's disease and macular degeneration fit together. Macular degeneration involves the nerve cells in the eye, while Alzheimer's disease involves the nerve cells in the brain. These cells must have a lot in common. In fact there are some common cellular mechanisms involving brain cell and retinal neuron degeneration. Some of the insults are related- smoking, build-up of lipids, aging- and this influence the course of both diseases. The lessons we learn from AMD will have some application to neurological disorders, like Parkinson's disease and Alzheimer's disease. The NIH is trying to take advantage of this and try and support the best science along these lines.

Paul Sieving MD PhD

Now: Director of the NEI since 2001

Formerly: Paul R. Lichter Professor of Ophthalmic Genetics and Director, Center for Retinal and Macular Degeneration, at the Department of Ophthalmology and Visual Sciences, University of Michigan, Kellogg Eye Center, Ann Arbor, Michigan.

Education
Undergraduate:
Valparaiso University, Indiana, honours degree in history and physics
Graduate:
Yale University, M.S. in physics at Yale University
Yale University Law School, one year
University of Illinois Medical School, Medical Degree
University of Illinois Graduate School, Ph.D. in Biomedical Engineering

Dr Sieving completed his residency in ophthalmology at the University of Illinois. He did his post-doctoral fellowship in retinal physiology at the University of California, San Francisco, with the late Dr. Roy H. Steinberg. He did a medical fellowship in inherited retinal degenerations at the Massachusetts Eye and Ear Infirmary, Harvard Medical School, with Dr. Eliot L. Berson.

Prior to becoming NEI director he served on several NIH study sections to review grant applications, and on numerous editorial and advisory boards. He has received grant support from NIH and various foundations since 1982 to further his research.

Dr Sieving has received many awards and honours, including the Senior Scientific Investigator Award from Research to Prevent Blindness, the Alcon Award from the Alcon Research Institute, and he is listed as one of the "Best Doctors in America."

He continues to do research and clinical work. His interests include retinal neurodegeneration and the genetics of retinal disease.

ET: Genetic and genomic research would seem to be another area of common influences.

Sieving: Yes, this is a big one for the vision science community. There are dozens of cataract genes, and there are dozens of genes that affect the cornea. Genetics in this field started with neuro- and retinal degeneration, but at this point we are looking at genetic roles in all parts of the visual system. We know in strabismus, for example, that genetic conditions lead to fibrosis of muscle. We know many genes are involved in glaucoma. The question is how do you put the story together? Now, instead of talking about glaucoma genes, we are talking about five different kinds of glaucoma, all with different gene involvement. We are in a very interesting time in history when we are moving from knowing very little about the genetic basis of disease to knowing enough to make it complicated but not enough to put the whole story together. In fact, there are more than 400 genes known that cause eye disease. And the number is increasing. We see opportunity here. This research will lead to gene therapy, where we can remove a faulty gene or put in a working copy of a gene, or replace a missing protein.

ET: The NEI seems to support a lot of research with immediate therapeutic potential. What about blue-sky research? Do you attempt to direct some grants towards the more distant horizons of research?

Sieving: Yes we do. It is an interesting process to look at how funding decisions are made. There is a spectrum of opportunities. There are some areas, such as retinal prostheses research that have a gee whiz factor, a gut level appeal, which we do support. We recognise that it is a longer time scale. But even in that area there are more immediate and practical opportunities. For example we would like to know whether retinal ganglion cells continue to work even when the photoreceptors are dead. These clever experiments, such as retinal chip implants, build into a future dream, but they are also designed in such as way as to yield some practical near term information. At one point while I was at the University of Michigan I worked as a peer scientist reviewing grants. You would look at the nuances, and try and figure out what the scientific aspects of an application could be. Those are the grant applications that get the attention, and the funding.

The first screen on which studies are funded is done by peer review. And the final screen as well. We rely on the wisdom of people who have spent their lifetimes working in a given field to make first cut whether a study is worth pursuing or not. Ultimately another limitation or winnowing is the budget. If we had an unlimited budget we would probably study unlimited things. But we have limited resources. Even $700 million doesn't go forever. We literally had one dollar left over last year.

ET: In some cases you may fund a large-scale clinical trial, such as OHTS (Ocular Hypertension Study), that yields significant conclusions. But is it clinically useful information? Is there any follow-through from carefully designed clinical trials to the real world clinical setting?

Sieving: One thing that came out of OHTS and other recent glaucoma studies is the realisation that pressure makes a difference. Lowering pressure in cases of glaucoma produces benefits. If you have low-pressure glaucoma but are losing vision, lowering IOP further produces benefits. So if you do a sort of meta-analysis of the concepts of glaucoma trials, you can triangulate a set of answers that somehow pressure in the eye is better when lower. This suggests there is some mechanism in the eye that couples pressure into a signal or pathway that ultimately damages ganglion cells and results in glaucoma.

As a next step, I would like to see a set of thoughtful glaucoma specialists get together and have them brainstorm on what could move therapy forward, or to decide what the next set of questions is. The clinically astute people should be in the same room with the basic biologists who think about how ganglion cells work so that there is some cross talk that will stimulate both to converge on something that might prove useful for lab work or clinical trials.

In practical terms, one interesting model is PEDIG (The Paediatric Eye Disease Group). Taking a very practical approach, a PEDIG study asked if six hours or two hours of patching was better for amblyopia. When I trained 25 years ago, we learned that you need to patch six hours a day or longer, yet this study asked a question that could be answered in physicians' offices. The answer- that length of patching didn't really seem to matter. This leads to more questions about treating older children and even adults with amblyopia. The PEDIG study showed how wonderfully plastic the visual system is. You can patch an eye for two hours per day and you modify how the brain works. It is remarkable.

ET: In some cases, NEI-funded extramural research involves a partnership with pharmaceutical companies. For example, Bausch and Lomb provided the supplements used in AREDS (Age-Related Eye Disease Study). What kinds of guidelines are in place regulating interactions with industry?

Sieving: We work under rules mandated by the US Congress regulating the interaction between NIH and industry. The details are contained in huge stacks of documents. Some of those regulations pertain to money that goes through NIH to a university, and how that money is allocated when commercial venture is involved. In general, we recognise that companies bring resources and skills that NIH or university scientists often may not have, so we look to complement the skill sets. Pharmaceutical companies are important players and collaborators in developing the information that leads to new medicines. The NIH office of technology transfer oversees these relationships.

ET: The NIH recently received some negative publicity regarding apparent conflicts of interest between researchers and commercial interests. This resulted in a set of strict new guidelines for NIH employees (most recently updated on August 25, 2005). Do you think the new guidelines could affect recruiting?

Sieving: All of NIH is wondering how this is going to play out. There are concerns that retention could be difficult. It is documented at this point that a number of people who thought they were coming here are having second thoughts. The long-term effects are not yet known. Ethics is very important at NIH. We have 17,000 people working at NIH, and invariably there will be problems, but I'm certain that the overwhelming majority of those working here are thoroughly ethical.

New NIH ethics guidelines launched

The US National Institutes of Health, which includes the National Eye Institute, announced new regulations regarding relationships between its researchers and outside parties. The release of the new guidelines, mandated by NIH director Elias Zerhouni MD, follows a period of turmoil at the NIH after an investigation revealed significant conflicts of interest with some researchers.

An internal investigation revealed that 44 researchers had violated conflict of interest rules. Violations concerned relationships with outside companies, inappropriate consulting arrangements and incomplete disclosures of potential conflicts of interest.

Dr Zerhouni banned such activities in February 2005, but many researchers complained that the new restrictions went too far, particularly on the question of stock ownership.

The regulations were developed by the Department of Health and Human Services in close collaboration with NIH, and the Office of Government Ethics. The new guidelines spell out the requirements for reporting of certain financial interests, stock divestiture, outside activities, and awards.

"We have a balanced set of conflict of interest rules that protect the integrity of NIH and its ability to provide the American public with an unbiased and trusted source of scientific and health information, while preserving our ability to recruit and retain world class scientists and staff," said Dr Zerhouni.

The new rules affirm a basic prohibition on outside consulting by NIH staff with substantially affected organisations, such as pharmaceutical, biotechnology or medical device manufacturing companies, health care providers or insurers.

Senior employees (along with their spouses and children) are required to divest all holdings in substantially affected organisations in excess of $15,000 per company. Less senior employees may be required to divest if, after review, a potential conflict resulting from their holdings or those of their spouses and minor children would impede their ability to do their government job.

The guidelines stipulate that receipt of monetary awards from outside sources will continue to be contingent upon prior approval and be limited to awards that have been determined through a pre-screening process to be bona fide. Senior employees cannot receive cash awards from donors who have matters pending under their official responsibility.

Under the new regulations, NIH scientists will be allowed to engage in compensated academic outside activities such as teaching courses at universities, writing general textbooks, performing scientific journal reviews or editing, and providing general lectures to physicians and scientists as part of a continuing professional education program. NIH scientists can also practice medicine.

Elias Zerhouni

US National Eye Institute continued...

Inside the NEI

Device for studying eye movements

This year the National Eye Institute expects to provide approximately two-thirds of its $700 million budget in 1,600 grants to extramural researchers at universities, hospitals, and research institutions. These grants cover all aspects of vision science and include projects outside of the US, including Europe and Asia.

The NEI's extramural research activities are organised into six areas: retinal diseases; corneal diseases; lens and cataract; glaucoma and optic neuropathies; strabismus, amblyopia, and visual processing; and low vision and blindness rehabilitation.

However, the NEI also reserves some ten percent of its research budget for intramural research. Situated in several buildings on the Bethesda, Maryland campus of the National Institutes of Health, the NEI researchers work in basic and clinical science, with bench science taking place only steps away from the NIH medical center. In addition to staff scientists and administrators, the halls are crowded with post-docs, visiting scientists and undergraduate interns. It is an international mix, with staff and fellows from the Americas, Asia, Africa, Europe and Russia.

Frederick Miles PhD directs the oculomotor research section. He is interested in early cortical processing of optic flow information in humans. He uses very sensitive eye tracking equipment created in the lab to measure eye movements in healthy and unhealthy patients. His lab has discovered three visual reflexes which they believe act as backups to the vestibulo-ocular motor reflexes when a person is in motion. These reflexes help maintain ocular stability and binocular alignment. He recently determined that treatment with the glutamate antagonist memantine could restore useful vision in a multiple sclerosis patient with ocular palatal tremor. Robert Wurtz PhD and Lance Optican PhD are also important contributors to research on visual perception and eye movement at NEI.

Robert Nussenblatt MD heads the clinical immunology section. He is interested in the cellular mechanisms of ocular inflammation particularly as they apply to uveitis. Researchers at his lab recently reported that intravitreal injection of the cytokine IL1ra suppresses autoimmune uveoretinitis in an animal model. The researchers suggest that intravitreal delivery of IL-1Ra may have clinical application in uveitis therapy. An NEI clinical study is now underway of treatment of active anterior uveitis using daclizumab (Zenapax, Hoffman La Roche).

The molecular mechanisms section, led by Dr T. Michael Redmond, has been involved in some of the key recent events in the genetics of vision research. This lab first demonstrated the role of RPE65 gene in Leber congenital amaurosis, setting the groundwork for another group that was able to restore vision to experimental animals with LCA. Another group has just reported that the RPE65 gene product is isomerase -the enzyme responsible for regenerating the photoreceptor molecule rhodopsin during light perception.

Bench meets bedside at the recently expanded NIH Hatfield Clinical Research Centre, the largest hospital in the world dedicated to clinical research. The ophthalmology section includes 12-14 doctors, four research fellows, eight nurse clinical trial coordinators as well as clinical nurses, techs, photographers, and administrators.

"We see more than 11,000 outpatients each year. We have 39 active protocols ongoing. Patients come in for evaluation, treatment and follow-up. All associated medical care is free, with lifetime follow-up," said William O'Donnell, MSHA, Clinical Operations Manager at NEI.

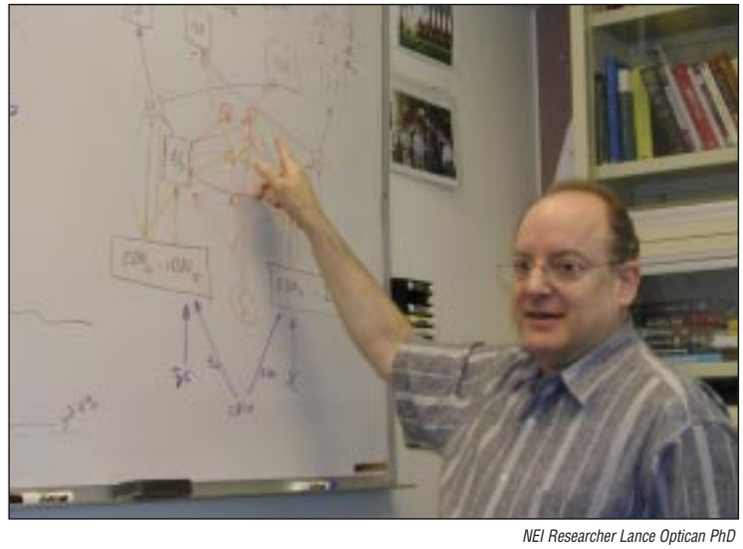
On any given day, patients will be visiting the centre to participate in diagnostic studies of dry eye, diabetic macular edema, cataract, gene therapy for retinal vascular and genetic eye diseases, or laser treatment of neovascular AMD.

A sampling of active protocols at NEI:

-A Randomised Trial Comparing Intravitreal Triamcinolone Acetonide and Laser Photocoagulation for Diabetic Macular Edema

-The Systemic Immunosuppressive Therapy for Eye Diseases (SITE) Cohort Study, which will evaluate directly whether immunosuppressive therapy for ocular inflammatory diseases is associated with an excess risk of mortality and of cancer.

-A dietary supplement study that will explore whether taking the vitamins lutein and zeaxanthin, with or without Omega-3 fatty acid (docosahexanoic acid), will change the amount of lutein and zeaxanthin in the blood among people with age-related macular degeneration.



NEI Researcher Lance Optican PhD

Hatfield Clinical Research Center, NIH