Optimism Pervades Parkinson's Conference

Over the week of 25–28 August 2001, a group of great minds thought alike in Colorado Springs, Colorado—epidemiologists, neurologists, and scientists from many other fields gathered to review the state of the science regarding Parkinson's disease (PD).

The conference was sponsored by the University of Arkansas for Medical Sciences and supported by numerous private and federal research facilities including the NIEHS. The participants came with a great sense of anticipation and hope, as recent research has given a new boost to the study of PD. Donato Di Monte, director of basic research at the nonprofit Parkinson's Institute of Sunnyvale, California, and a conference cochair, put it this way: "We're no longer at a stage where we wonder whether to look at environment or look at genes. . . . In a few years we might be able to come together and be talking about real issues like how to implement these ideas in prevention and treatment."

A Multifaceted Brain Disorder

Because the conference was attended by scientists from many different disciplines tackling PD from many different angles, several speakers reviewed the chemical, biopathologic, epidemiologic, toxicologic, and neurologic aspects of PD. PD is just one of many similar disorders grouped under the name "parkinsonism." Sufferers may have tremor in their limbs, jaw, or face, and rigidity in their limbs and torso. They may move slowly with jerky motions and suffer impaired balance and coordination. PD is a progressive disorder that most often begins after age 55. It is incurable. However, symptoms can sometimes be treated with drugs such as L-dopa or with treatments such as deep brain stimulation, in which an electrode is implanted in the brain in order to standardize the electric current fueling the brain's different processes.

PD symptoms are caused by the loss of cells in the substantia nigra, a part of the brain that controls movement. Nigral cells produce the neurotransmitter dopamine, and dopamine controls signalling to the motor cortex, which initiates smooth movement. Once dopamine has been depleted by about 80%, the jerky, uncontrolled movements characteristic of PD begin to appear. It is not yet known whether PD patients are born with less dopamine, whether dopamine loss accelerates with age, or whether loss is secondary to some other process.

Postmortem examinations also reveal that PD patients typically develop Lewy bodies, microscopic structures containing the protein α-synuclein, in the substantia nigra. Scientists still aren't sure what role Lewy bodies play in PD. It is possible that they cause cell death, or that they serve as corrals, concentrating toxicants in the brain. Whether they cause PD or are caused *by* PD is unknown.

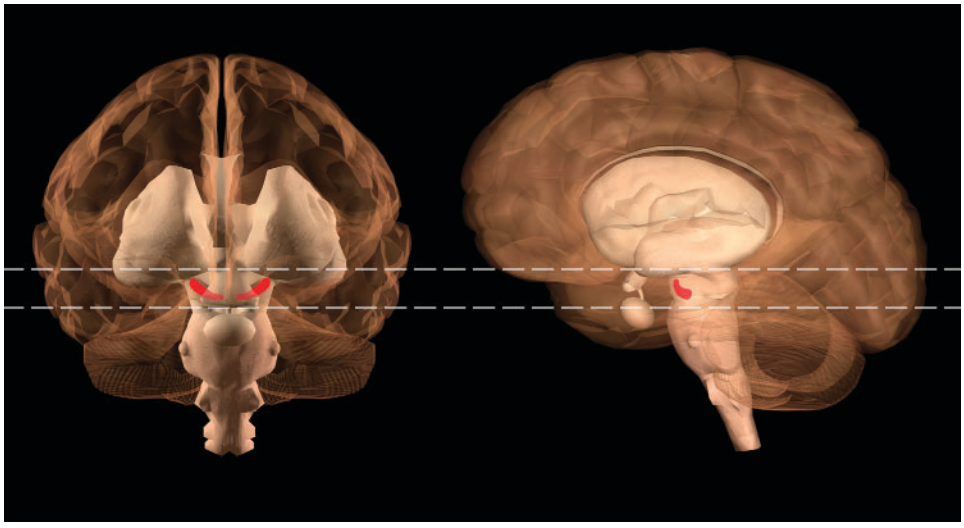
Interest in PD as a possible environment-related disease grew after the publication of a paper by Parkinson's Institute researcher Caroline Tanner and colleagues in the 27 January 1999 issue of the *Journal of the American Medical Association*. Tanner's results showed that fraternal and identical twins did not show appreciably different concordance rates of PD. As genetics did not appear to be driving the disease, the researchers suspected there is a strong environmental component.

Although, as Di Monte said at the conference, "aging is the only unequivocal risk factor for PD," several environmental factors correlate with PD incidence. These include exposure to hydrocarbon solvents, viral infections such as encephalitis, high dietary fat, high iron levels, depression, and head injury. Exposure to both single metals such as manganese and to mixtures of metals including lead, copper, and iron has also been implicated.

Pesticides have long been suspected of having a particularly strong link with PD. A 2000 study by Lorene Nelson of Stanford University, with colleagues Tanner and Stephen Van Den Eeden of the Kaiser Permanente Medical Care Program of Northern California, showed a 70% increased risk of PD among users of in-home insecticide and garden herbicides. (No dose–response relationship was clarified.) These findings were presented at the 2000 annual meeting of the American Academy of Neurology in San Diego, California. The widely used paraquat, maneb, and heptachlor have been especially targeted as pesticides implicated in PD, and paraquat and maneb in combination have been shown in mouse studies to cause greater locomotor disturbance than either pesticide by itself.

Other studies have demonstrated an inverse correlation between certain environmental agents and PD incidence, suggesting the possibility of neuroprotective effects. Several of these agents involve so-called vice behaviors. Over 35 case–control studies—including prospective studies, where recall bias is not an issue—have shown that the risk of PD is lower in smokers than in nonsmokers. Smoking can also reduce many of the symptoms of PD. Other studies have shown that caffeine boosts the effects of L-dopa in laboratory animals, and that drinking beer and spirits (but not wine) correlates with a 30–40% reduced incidence of PD.

Intriguing theories about the possible connection between PD and vice behaviors abound. Perhaps people who are predisposed to PD are also predisposed to avoid high-risk or pleasurable behaviors, such as smoking. Animal studies have already shown that dopamine depletion leads to decreased exploratory behavior. Similarly, lower brain dopamine concentrations in people predisposed to developing PD might lead to a



Pinpointing PD. Parkinson's disease symptoms are caused by the loss of cells in the substantia nigra (in red), a part of the brain that controls movement.

LifeART, Christopher G. Reuther/EHP

reduced propensity for novel or pleasurable behaviors, so that they would smoke or drink less than others. This would make it appear that smoking and alcohol use protects against PD—which may or may not be the case.

Vice behaviors do not have a monopoly on lowering risk, however. Vitamin E and other dietary antioxidants also have been associated with lowered incidence. The effect is noted in legumes containing these compounds, however, rather than in dietary supplements. Another study, in Germany, found no correlation between vitamin E and PD, but did note lowered risk with intake of niacin, beta carotene, and ascorbic acid. (Niacin is also found in coffee.)

Defining a Course of Action

Specific research directions identified at the conference include identifying specific gene mutations—perhaps, for example, of the α-synuclein gene—to yield a PD-vulnerable phenotype. Defining the role of the Lewy body in PD is another important step. "Ultimately a combined approach utilizing a highly interactive interplay between epidemiology, genetics, and basic science will be required to unravel the cause of PD," said keynote speaker J. William Langston, founder and president of the Parkinson's Institute.

Participants discussed where research dollars could be spent most effectively in PD research. Suggestions included looking for clinical pathologic symptoms of PD, gene profiling, studying the cellular mechanisms behind neurodegeneration, building well-characterized brain banks, using microarray technology, and sharing data and resources.

Epidemiologic studies are critical for identifying risk factors for PD that can then be studied in animal models. But such studies are difficult because the disorder is relatively rare—according to the Parkinson's Institute, it afflicts about 200 out of every 100,000 people. There is no registry for PD cases, and PD is rarely listed on death certificates as a cause of death. There is currently no diagnostic test or biomarker that can be measured for living patients, and the long preclinical period means many people who are in fact affected may die before they show PD symptoms. Finally, PD is usually a late-life disorder, and identifying possible relevant environmental exposures has to date been necessarily retrospective.

Some of these difficulties are being addressed in a study described at the conference by NIEHS epidemiologist Freya Kamel, Tanner, and colleagues. Kamel and Tanner will perform a nested case–control study to prospectively examine the epidemiology of PD among farmers who are already participating in the ongoing Agricultural Health Study. Several earlier studies looked at agricultural work and PD among general populations, but this study has the advantage of studying the disorder in a population with more consistent exposure to potential PD risk factors such as pesticide use. The researchers will take detailed information on the subjects' pesticide use, life style, and health status. Subjects will also undergo a neurologic evaluation and pesticide and metal blood assays, and mutations in their DNA will be studied. In addition, the researchers will look for the presence of the soil microbe *Nocardia asteroides*, which has been shown to induce parkinsonian symptoms in lab animals.

Many other questions wait to be answered. Why do more men develop PD? Is it a hormonally related disorder? Is it X-linked? Or are occupational exposures to blame? A study of PD cases in Olmsted County, Minnesota, showed a sharp spike in cases among women during the years 1945–1954 and a more gradual increase after 1964. Might this be due to women's changing role in the workplace since World War II? Why do PD rates differ among white, black, and Asian populations? And what is it about aging that makes it such a prominent risk factor for PD?

NIEHS Goes a Step Further

The NIEHS currently supports 24 PD-related research projects through its extramural Environmental Health Sciences Centers Program. At the beginning of the conference, Olden announced that the institute is going a step further by establishing a consortium to study gene–environment interactions in PD. By learning more about how environmental exposures and genetic predisposition work together to cause PD, scientists can begin to develop effective approaches to disease prevention, diagnosis, and treatment. Olden hopes the consortium will be funded by the end of fiscal year 2002; a request for applications was in the process of being released at the end of November. Eventually the consortium will include other federal agencies as well as private research organizations.

The consortium is intended to extend and integrate existing funded research in PD, increase communication among clinicans, geneticists, epidemiologists, and basic science researchers in the field of PD, and support the translation of research findings from the laboratory to the clinical setting. By enhancing communication among scientists with similar goals, promising lines of investigation can be identified and pursued more promptly and effectively, and granting agencies can respond more quickly to research opportunities as they arise. "Once we agree on concept and scope," said Olden, "we can develop a more detailed strategic plan that includes budget and time lines."

In the meantime, the conference has provided a solid starting point for future collaborations. Said Olden, "The science and interaction between scientists [at the conference] has been outstanding. Typically people listen, and you have one or two questions, but here there has been lots of discussion. The science has already come a long way. If we can start working on some of the points raised here, I hope we can start making some progress in the next three to four years." **–Susan M. Booker**

NIEHS and ACC Establish Grant Program

On 26 July 2001 the NIEHS and the American Chemistry Council (ACC) signed a unique memorandum of understanding that will provide $4 million over the next two years to conduct multidisciplinary extramural research on potential developmental toxicants. The research will specifically study mechanisms of action, using tools such as DNA microarrays and genetically sensitized animal models to look at cellular networks of responding genes, help define important target molecules and pathways for toxicity investigations, and provide clues to future biomarkers of toxic exposure and effect. Says NIEHS director Kenneth Olden, "This [memorandum of understanding] is a collaboration between government and industry to improve the health of the American people by improving the quantity and quality of the data on potential developmental toxicants that are available for use in the risk assessment process."

The ACC, a chemical industry trade group, will provide funding for the grants through its Long-Range Research Initiative program, established in 1999 to study the effects of chemicals on humans and wildlife.

The joint NIEHS–ACC grant program is expected to fund about 15 exploratory research grants by next spring.