the centers participating in the initiative.

The radiograph, in which a patient's knee is X-rayed while standing up, is the current standard for analyzing cartilage loss, but smaller studies have suggested that MRI may be a more reproducible technique. In addition, patients will provide blood samples and medical histories. Data from four clinical research centers will be sent to a coordinating center at the University of California, San Francisco, which will render the information anonymous and assemble it into a publicly accessible database.

Although the companies are contributing \$23 million to the effort, Katz insists that they will not be given preferential access to data. Instead, the companies will benefit in less direct

ways. "None of them by themselves could generate such a resource ... and none wants other companies to be able to have such a resource that is exclusive." By supporting the Osteoarthritis Initiative, the companies may gain useful biomarkers to develop blockbuster drugs, while reducing the risk that their competitors will gain an edge.

"What we're hoping will happen is that scientists in academic health centers as well as people in industry ... will be able to somehow utilize this database and apply for the use of materials like serum for validation studies of progression. Wouldn't it be wonderful to have a serological marker for osteoarthritis?" says Katz.

Although more than half the US population over the age of 65 has evidence of osteoarthritis in at least one joint,

the causes and progression of the disease are poorly understood. Hochberg says, "The general feeling is that the primary lesion lies in the articular cartilage, with a loss of the normal homeostasis between cartilage formation and breakdown." As the equilibrium shifts, the joint loses cartilage, causing pain and a loss of joint mobility.

Beyond this general outline, though, the progression of the disease varies tremendously, making clinical studies difficult. "Some people may have radiographic changes, like a decreased joint space where the cushion of one bone starts getting closer to the other bone, but in some there's no accompanying pain, [while] in others where there's very little degeneration there may be pain," says Katz.

Alan Dove, Philadelphia

Pesticide-Parkinson link explored

To understand the link between toxic environmental agents and Parkinson disease (PD), the National Institute of Environmental Health Sciences (NIEHS) has awarded \$20 million in grants to three research centers over the next five years. The centers—the Parkinson's Institute, Emory University and the University of California at Los Angeles (UCLA)—will act as a consortium, collaborating and coordinating research projects, bringing together epidemiologists, basic scientists and human geneticists.

"What is unique about the program is that it is very prescriptive as to the tightness of those collaborations," says Cindy Lawler, NIEHS scientific program administrator. The structure of the consortium is such that an epidemiology study that uncovers an association between a specific agent and PD in humans can be translated rapidly into a laboratory study that investigates the mechanism of toxicity and vice versa. "Hopefully it will set the tone for tackling the disease," says PD researcher Ole Isacson from Harvard Medical School.

The initiative has given new impetus to the field. William Langston, founder and CEO of the Parkinson's Institute, says, "What the NIEHS is saying [with the latest initiative] is that the research is far enough along to become proactive." NIEHS estimates that it will provide \$12 million in funding for PD research in 2002, a doubling of its FY2001 support.

A number of large population studies suggest that people with jobs that expose them to pesticides have a higher risk of developing PD, a neurodegenerative illness marked by the death of the brain cells that produce and release dopamine. However, "there has not been a specific class of pesticides or specific pesticide linked to PD," says Harvey Checkoway, an epidemiologist at the University of Washington.

"There is no smoking gun."

This "gun" is what several projects that will receive funding are trying to find. UCLA epidemiologist, Beate Ritz, is conducting "the largest prospective study, looking at both occupational and residential exposure." The work will take advantage of the fact that California law requires that all agricultural application of pesticides are reported, thereby providing a detailed record of what people have used and where.

The proof of concept that pesticides might be involved in PD comes from animal studies. Timothy Greenamyre of Emory University has shown that admin-

istration of a pesticide used in organic farming and home gardening, rotenone, results in selective degeneration in rats in the same regions of the brain affected by PD in humans. But rotenone is not the first chemical to produce PD in animals. In 1998, Langston's team found that

MPTP, a chemical in a synthetic form of heroin, could faithfully reproduce PD both in animal models as well as individuals taking the drug. Rotenone and MPTP, as well as paraquat, another pesticide linked to PD, act by inhibiting mitochondrial function. A defect in mitochondrial function is also seen in patients with PD.

An important finding in Greenamyre's study was that the rotenone-treated rats developed spherical clumps of protein known as Lewy bodies in the substantia nigra—a telltale sign of human PD. The clumps consist of the protein α -synuclein, which is associated with inherited forms of PD. "The key finding from all these studies is that these genetic and environmental factors are producing some kind of toxic process that leads to [a common] degeneration process," says Isacson.

Laura Bonetta, Bethesda

Rotenone exposure causes loss of dopamine neurons (right).

Courtesy: J. Timothy Greenamyre