Big First Scored with Nerve Diseases

Therapy for Parkinson's disease—and possibly other neurodegenerative diseases—is on the verge of a major change in the United States, the result of a significant clinical trial published this week

A STORY THAT BEGAN 7 years ago amid the California drug culture today ends with the results of a clinical trial that could dramatically improve the treatment of Parkinson's disease in the United States. On page 519 of this issue, neurologists James Tetrud and William Langston report that Deprenyl, a monoamine oxidase inhibitor, substantially slows the rate of neurodegeneration in parkinsonian patients. "The magnitude of the effect is much greater than we could have hoped for," says Langston. "I suspect that very soon Deprenyl will find a place in the early treatment of Parkinson's disease."

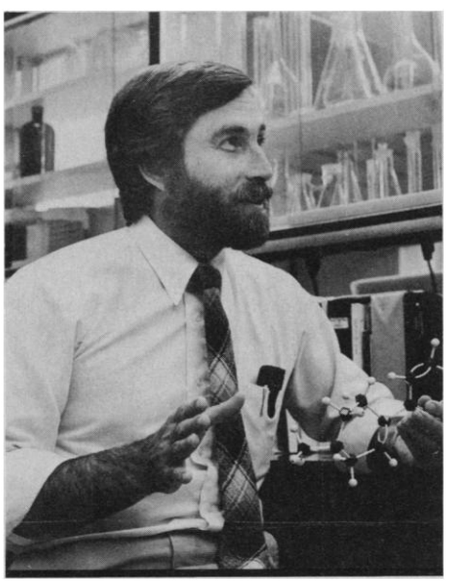
The tremors and lack of muscular control that are so characteristic of Parkinson's disease are the result of the progressive loss of nerve cells in an area of the midbrain known as the substantia nigra. The job of these cells is to produce the neurotransmitter dopamine, and so the normal treatment for Parkinson's patients is to give them levadopa, which substitutes for the reduced levels of dopamine in the diseased brain.

Dramatic though the therapeutic effect of levadopa is, it usually offers only a temporary respite from the symptoms of neuron loss. "Slowing down the rate of degeneration of nigral neurons would be an even better therapy than levadopa, at least in the first instance," says Langston. "And we seem to have achieved that."

This result is important enough in the restricted realm of Parkinson's disease, but it is more than that. "No drug treatment had succeeded in slowing the rate of neuronal loss in *any* neurodegenerative disease," adds Langston. "This may be a first."

So what does the California drug culture have to do with landmark research in neurology? "The first link was forged in 1982 when a young man in Silicon Valley was sloppy in his synthesis of a synthetic heroin," explains Langston. "That sloppiness led to the presence of a contaminant, MPTP, which by an extraordinary trick of fate is highly toxic to the very same neurons that are lost in Parkinson's disease."

Suddenly, young people started to turn up at various neurology clinics in the area, displaying varying degrees of parkinsonian symptoms, some so severe as to render the individual paralyzed and speechless. Since Parkinson's disease is essentially a condition of middle to old age, and only very rarely afflicts people in their twenties: doctors knew something extremely odd was going on. But it took a while before MPTP was identified as the culprit in this medical mystery, the discovery being made by Langston and his Stanford colleague Ian Irwin. That revelation ignited a revolution in research on Parkinson's disease.



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—William Langston

"MPTP gave us the best model system we have for studying a parkinsonian-like condition in animals," says Langston. "It's been a crazy 7 years for Parkinson's research." In the wake of his success Langston broke his ties with Stanford Medical School and established the California Parkinson's Foundation, San Jose. There, and elsewhere in the country, the race to understand how MPTP worked and what it might reveal about the natural disease inspired frenzied competition and cooperation among scores of research groups.

The key discovery that led to the recent clinical trial was made by chemists, particularly Neal Castagnali, Anthony Trevor, and their colleagues at the University of California at San Francisco. MPTP, it turned out, does not itself inflict damage to the brain: it first has to be converted to a metabolite known as MPP+. Midway through 1984, and just days before a major MPTP conference, Castagnali and his colleagues showed in a test tube experiment that addition of a certain monoamine oxidase inhibitor blocked the chemical conversion of MPTP to MPP+.

This result sent half a dozen research teams—including Langston's—scurrying to their labs to do the obvious experiment: to see if monoamine oxidase inhibitors could block the devastating nerve damage inflicted by MPTP in experimental animals. It did. "That really lit things up," remembers Langston. "And it also helped make sense of something that had been puzzling us for about a year."

That puzzle had been a report from a team of European researchers that the monoamine oxidase inhibitor Deprenyl, given to Parkinson's patients in combination with levadopa, reduced disease symptoms and even increased lifespan. There were drawbacks with the European study, however, the principal one of which was that it was retrospective, making proper controls impossible. "But, combined with the MPTP story, it pointed us in the direction to follow," says Langston.

That direction was a double-blind, prospective trial of the efficacy of Deprenyl in patients in the early stages of the disease. Plans for what would be a relatively small clinical trial immediately got under way at Langston's San Jose lab, but were soon threatened with being knocked off track.

"We were 6 months into setting up our trial when Ira Shoulson proposed a much more ambitious effort," explains Langston. Shoulson, a neurologist at the University of Rochester, proposed a project that eventually developed into the so-called DATATOP study, an 800-patient, 28-center, clinical trial funded to the tune of $10 million by

the National Institute of Neurological and Communicative Disorders and Stroke. This study, the results of which are still under wraps, is also testing the effects of vitamin E on the rate of neurodegeneration.

"For a long time it was not clear that DATATOP would get funded, so we decided to continue with our much smaller trial," says Langston. In many ways the design of Shoulson's larger trial benefited from the early experience of the San Jose study. "Our trial has turned out to be something of a pilot study for DATATOP. We look forward to seeing if our results are confirmed." Although Shoulson declines comment on the outcome of DATATOP, rumors are that it echoes the San Jose study.

So what do these results imply? On a practical level, they mean a cost saving of about $340 million a year in the United States: for every extra week that Parkinson's patients can remain functional enough to work, $10 million are saved in the balance of taxes and disability payments. On the more academic level of understanding the disease, there are still many possibilities.

"Bill Langston would like to think that these results imply the existence of some kind of environmental toxin—something like MPTP—that causes neurodegeneration in Parkinson's disease," comments Roger Duvoisin, of Rutgers Medical School. "I doubt that this is important in the etiology." Duvoisin is in the middle of a reexamination of some twins studies that, he says, indicates a substantial genetic component in the cause of Parkinson's. By contrast, the University of British Columbia's Donald Calne, who is also involved with the twins studies, speculates that the genetic component is small—"perhaps 25%."

What really excites Calne, however, is that the results of the San Jose trial might be pointing to a rather general mechanism in neurodegenerative diseases, including Alzheimer's disease and amyotrophic lateral sclerosis. "The etiology of all these diseases might involve aberrant free-radical formation," says Calne. "Deprenyl treatment is one way of halting or slowing down radical formation, but there are other agents that could be tried as well."

If Deprenyl is so effective, why didn't it halt neurodegeneration completely? "One possibility is that the etiology involves several factors, with free-radical formation being only one of them," suggests Langston. "Another is that we didn't use high enough doses of Deprenyl. Our plan now is to rerun the trial using different dose levels, some lower, some higher. Whatever happens in these new studies, we've achieved more here than we could have hoped for in the beginning." ■ ROGER LEWIN

Deep Holes Yielding Geoscience Surprises

Sinking scientific boreholes in the continents is testing geology and geophysics with unexpected, sometimes disturbing, results

WHEN WEST GERMAN GEOSCIENTISTS came to the Oberpfälz Forest, they were not interested in the Bavarian scenery or the Wagnerian music festivals at nearby Bayreuth. They were there to drill the deepest hole in the world—one to 14 kilometers. The scientific rationale for this heroic venture was the testing of ideas about the crustal suture where an ancient collision fused two segments of the European continent.

By choosing the Oberpfälz site, the German researchers thought they would avoid dangerously hot rock. The fear of too much heat had scared them off other sites because it would bring the drilling venture to a premature end. But now, after drilling a 3.5-kilometer pilot hole, they have found that they are going to hit the very problem they so carefully planned to avoid.

Instead of the expected 80°C at the bottom of the hole, it is 118°C, outside the range predicted. As a result, plans for the record-breaking hole have been scrapped. The target depth of the so-called KTB hole has been scaled back to a more modest 10 kilometers—assuming, of course, that the new temperature predictions are better than the first ones.

This chastening experience is just one example of the many discomforting surprises geoscientists around the world are encountering as they test hypotheses about the earth's crust through drilling. "Every time we drill a hole," says Mark Zoback of Stanford University, "we find the unexpected. That's exciting but disturbing."

Scientific surprises are inevitable, even desirable, as geoscientists venture into unknown territory by drilling ever deeper into the crust. But, as in the Oberpfälz, big surprises—or too many little ones—can mean less science than promised at the same or even higher costs. That is no argument to quit drilling. Quite to the contrary, it is becoming increasingly apparent that drilling provides a necessary calibration of geoscience tools against reality as much as it directly tests ideas about how the crust behaves. It is just that now older but wiser geologists and geophysicists will be working to reduce the number of surprises by honing the tools that predict what lies below the surface.

L. Younker/SPOT Image Corporation

A target. *The hydrothermal system of Valles Caldera, a 25-kilometer volcanic scar in New Mexico, has three holes drilled.*

Too late though, for French researchers. A team under the Deep Geology of France Program came up against a piece of unpleasant reality that they reported at last month's International Geological Congress in Washington. Contrary to their expectations, they failed to find a magnetized body of rock at the bottom of their recently completed Sancerre-Couy borehole 150 kilometers south of Paris.