Brain scans show interferon slows MS attack

By documenting changes in the brain with magnetic resonance imaging (MRI), neurologists have gathered evidence that a genetically engineered drug slows the progression of multiple sclerosis (MS).

Last week, an advisory panel of scientists recommended 7 to 2 that the Food and Drug Administration approve a form of beta interferon for treating people with relapsing-remitting MS, which affects up to two-thirds of the 300,000 U.S. residents with the disease. They suffer from unpredictable flare-ups that cause vision problems, memory loss, tremors, partial paralysis, and other neurological symptoms. Often, the disease gradually worsens to a chronic, debilitating stage as it destroys more and more tissue in the central nervous system.

While several medications alleviate some symptoms, this interferon is the first drug deemed capable of slowing the frequency of acute attacks, says Stephen C. Reingold, vice president for research and medical programs at the National Multiple Sclerosis Society in New York City. It may work by countering other immune system activity directed against the myelin sheath that coats nerve cells.

In a three-year clinical trial, researchers said, 338 volunteers at seven U.S. and four Canadian research centers injected the drug or a placebo into their leg muscle every other day. Neither the patients nor the doctors treating them knew whether they were taking the active drug. The participants kept daily diaries and visited the doctors whenever flare-ups occurred. They also underwent periodic MRI scans of their brains.

Participants taking high doses of beta interferon went an average of 295 days before their first flare-up, 142 days longer than those not on the drug. They averaged 0.84 attack per year, and about 31 percent had no attacks during the study. Those taking the placebo averaged 1.27 attacks per year, and just 16 percent of them suffered no flare-ups during the three years. Participants taking the drug also required fewer trips to the hospital and suffered fewer severe attacks, says neurologist Donald Paty, the study coordinator at the University of British Columbia in Vancouver. The most common side effects were flu-like symptoms and pain from injections.

FDA analysts point out that excluding patients whose attacks were not immediately verified by physicians and those who left the study early weakened the statistical significance of the results.

But MRI brain scans showed that the diseased area increased about 20 percent in MS patients taking the dummy drug but only about 7 percent in those taking moderate levels of the drug; it decreased 4 percent in those taking high doses. "This will be the first time that MRI has shown a real correlation with clinical outcome," Reingold says.

That helped convince the expert committee. "The MRI data make [the study] much more compelling and approvable," says Sid Gilman, a neurologist at the University of Michigan in Ann Arbor.

Reingold expects that clinical tests of new drugs for MS will rely increasingly on MRI evidence. Many neurologists have preferred to monitor participants' health and the development of symptoms, arguing that symptoms are what need treating. But symptoms sometimes disappear naturally or do not show up during a drug trial. "[This study] verifies what a lot of us have expected — that the MRI would prove to be the most sensitive way to evaluate treatment," says William A. Sibley at the Arizona Health Sciences Center in Tucson.

"If you can treat the [nerve damage], then you're treating the disease," adds Reingold.

Berlex Laboratories of Richmond, Calif., and Chiron Corp of Emeryville, Calif., developed the drug, called Betaseron. Other researchers are testing different interferon products against MS as well. — *E. Pennisi*

'Dwarf' mammoths outlived last ice age

Woolly mammoths, those icons of the ice age that most paleontologists assume died out around 9,500 years ago, survived in miniature form — or what passed for miniature among mammoths — until about 4,000 years ago on an Arctic Ocean island, according to new findings.

Mammoth teeth found in 1991 on Wrangel Island, located 120 miles off the coast of northeast Siberia, range from approximately 7,000 to 4,000 years old, report Andrei V. Sher and Vadim E. Garutt, paleontologists at the Russian Academy of Sciences in Moscow. The relatively small teeth suggest that Wrangel "dwarf mammoths" reached at most 70 percent of the size of their Siberian kin, the researchers say.

"[This is] one of the most extraordinary fossil finds of recent times," writes Adrian M. Lister, a biologist at University College in London, England, in a comment accompanying the new report in the March 25 NATURE.

He estimates that the Wrangel animals stood 6 feet high and weighed 2 tons, compared with 10½ feet and 6 tons for typical European mammoths.

The Wrangel finds may reignite debate over the reasons for the widespread mass extinctions of large mammals between 12,000 and 10,000 years ago, Lister notes. Some researchers contend that the waning ice age produced abrupt environmental changes that doomed many creatures. Others argue that human hunters, at least in North America, rapidly killed off many large-bodied species (SN: 10/31/87, p.284).

"This is a wonderful discovery, however we end up interpreting its significance regarding mass extinctions," remarks Paul S. Martin, an ecologist at the University of Arizona in Tucson, who favors the latter theory.

Sher and Garutt studied 29 adult mammoth cheek teeth found by Sergei L. Vartanyan, a paleontologist at Wrangel Island State Reserve. Five of them are comparable in size to mammoth teeth previously found in Siberia, the researchers contend. Radiocarbon dating places these five specimens at about 20,000 to 13,000 years old.

The remaining 24 teeth are considerably smaller and date from around 7,000 to 4,000 years ago. This confirms similar radiocarbon ages derived last year from more than two dozen mammoth tusk and bone fragments discovered on Wrangel Island, Sher and Garutt assert.

Radiocarbon dating of bone "can be tricky," Martin points out. But fewer soil contaminants seep into bone buried in cold regions, he says. And two independent laboratories produced nearly the same ages for tusk and bone samples, the Russian scientists note.

Siberian mammoths probably reached Wrangel Island during the ice age, when low sea levels created a land bridge to the mainland, Sher and Garutt theorize. By 12,000 years ago, that connection had been submerged.

Unlike nearby islands, Wrangel currently contains vegetation similar to that of ice age grasslands and may have provided a hospitable environment for mammoth survival, the scientists hold. Full-bodied mammoths then evolved into smaller forms on Wrangel, they suggest. Dwarf forms of other large animals existed on late-ice-age islands elsewhere, Sher and Garutt note.

Why the Wrangel mammoths shrank remains unclear, Sher says. Some Siberian mammoths showed body-size decreases by 12,000 years ago, a process that may have accelerated on Wrangel because of the genetic isolation of a small population under nutritional pressures, he suggests.

Scientific reconstruction of plant and animal histories on the island is now under way, Sher points out, as well as an anatomical analysis of large and small Wrangel mammoth teeth. — *B. Bower*

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