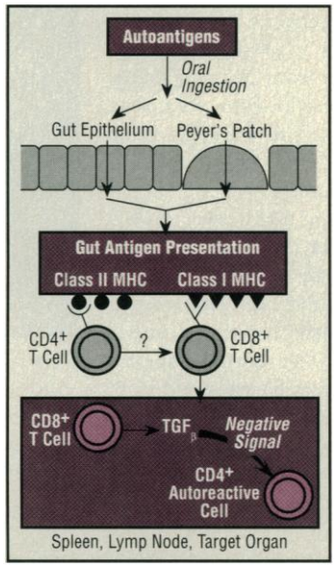
Testing of Autoimmune Therapy Begins

Clinical trials are beginning to ask whether autoimmune diseases such as multiple sclerosis can be treated by feeding the proteins that caused them to the patients

RESEARCHERS PURSUING ONE OF THE MORE venerable discoveries of immunology may have hit on a potential new strategy for treating diseases such as multiple sclerosis and rheumatoid arthritis that seem to be triggered when a body's immune system turns on its own tissues. They have found that they can suppress similar autoimmune attacks in lab animals by feeding them the protein antigens that triggered the abnormal reactions in the first place. Indeed, the animal results have been so promising that human trials of oral antigen therapy for multiple sclerosis and rheumatoid arthritis are already under way, and a trial is planned for uveitis, an inflammatory eye disease.

Currently, the autoimmune diseases are treated with broadly immunosuppressive drugs that leave the patients vulnerable to opportunistic infections. That problem has led immunologists to look for more precise therapies for the conditions. Many of the strategies they have been coming up with are high-tech—based on monoclonal antibodies or on synthetic peptides designed to block only those immune cells that initiate and carry out the abnormal attack. But antigen feeding, if it proves effective in the human autoimmune diseases, would be much easier to use than high-tech approaches, which require injections that will probably have to be administered in clinics or hospitals. "In the animal models, [antigen feeding] is clearly working as well as the other approaches. I think it's a very practical way of obtaining immune suppression," says Larry Steinman of Stanford University School of Medicine. This is high praise from an investigator whose own work focuses on the high-tech methods.



One route to oral tolerance. *An ingested protein may generate immunosuppressive (CD8) cells directly or indirectly.*

Although it might seem surprising that ingesting protein antigens can suppress immunity—other types of exposure tend to stimulate it—the idea has a long history in immunology. It originated in experiments done back in 1911 by H. Gideon Wells, says Howard Weiner of Harvard Medical School and Brigham and Women's Hospital in Boston, who heads one of the teams exploring the new therapeutic approach. Wells found that guinea pigs became resistant to anaphylaxis, a severe immunological reaction induced by injecting foreign proteins, if the animals were first fed the proteins for several weeks. In subsequent years, immunologists found other examples of such oral suppression. "A number of basic studies done by people over the years have shown that feeding antigens generates cells that suppress immune responses," Weiner notes.

The Harvard neuroimmunologist has been treating multiple sclerosis patients for about a decade and about 5 years ago he began wondering whether this natural form of immune suppression might help the patients. If so, he reasoned, it might prove considerably less toxic than the steroids and other drugs usually given to people with multiple sclerosis. In addition, it would be more specific than the drugs, because the suppression induced by feeding a protein works only for that protein, leaving other immune responses fully operative. "Antigen feeding works like a vaccine," Weiner says, "but you're vaccinating to get suppression, rather than immune stimulation."

To test his notion, Weiner and his Brigham colleague Paul Higgins turned to a commonly used animal model for multiple sclerosis, known as experimental allergic encephalomyelitis (EAE). Researchers induce EAE by injecting rats or other lab animals with myelin basic protein, a major component of the membranous sheaths that surround many nerve fibers. The injected protein triggers an immune attack on the myelin sheaths, causing nerve lesions and symptoms similar to those of human multiple sclerosis. Weiner and Higgins found that they could inhibit the development of both the lesions and clinical symptoms of EAE if they fed myelin basic protein to rats before giving them the injections. Also, at about the same time, an independent group, led by Caroline Whitacre of Ohio State University, obtained similar results.

Now the researchers could address the next question: would antigen feeding suppress other experimental autoimmune conditions as well? Early results suggest that it can. Take the eye inflammation uveitis, which can be induced in rats by injecting them with S-antigen, a protein isolated from the retina of the eye. "We're able to feed rats with S-antigen and prevent the disease," says Robert Nussenblatt of the National Eye Institute in Bethesda, Maryland, who collaborated with the Weiner group on the uveitis experiments. And several groups, including Weiner's, have found that feeding collagen, a prominent constituent of cartilage, can suppress the development of experimental arthritis. In all cases, the animals become tolerant only to the antigen they've been fed—not to any others.

Of course, the ultimate aim of the research isn't to prevent disease but to stop autoimmune disorders that are already under way. And recent work by Weiner and his Brigham colleagues Staley Brod and David Hafler suggests this might be possible. They have found that antigen feeding can ameliorate EAE in rats and guinea pigs after chronic symptoms begin. "We can suppress relapsing disease in animals after they have already had an attack," Weiner says.

Exactly how oral suppression works is not clear, especially in view of a puzzling discrepancy between results from the Weiner and Whitacre labs. Experiments done by Ofer Lider, a former postdoc with the Brigham group who is now at the Weizmann Institute in Rehovot, Israel, suggest that antigen feeding leads to activation of a class of immune cells, the CD8 cells, that can suppress the activities of other immune cells—possibly including those that would mount an attack on the antigen (also see

diagram). For example, Lider found that animals who have never been exposed to myelin basic protein can be made tolerant to it by injecting them with CD8 cells taken from animals fed the antigen. New results suggest, Weiner says, that the immune suppressive effects of the CD8 cells are brought about by their releasing transforming growth factor β, a cytokine that inhibits the activity of certain immune cells.

Whitacre, however, has a very different view of how feeding antigens might lead to tolerance. The Ohio State group has not been able to transfer tolerance from antigen-fed to unexposed animals the way the Weiner group has. Whitacre says that this and her other results lead her to believe that oral tolerance results from the specific deletion or inactivation of the immune T cells that respond to the antigen, rather than from the activation of suppressor CD8 cells.

Both groups are looking for ways to explain the discrepancy in their results. Whitacre notes that there are small differences between the way the two groups do their experiments, but she wouldn't expect them to account for the discordant findings. Weiner suggests that perhaps both suppressor cell activation and T cell deletion might be operating in oral tolerance, but even so that wouldn't explain why Whitacre failed to see tolerance transfer.

Whatever the precise mechanisms of oral tolerance, the researchers have been sufficiently encouraged by the animal results to begin human trials. Weiner and Hafler are just winding down one study in which 30 multiple sclerosis patients took a daily capsule of myelin purified from cow brains. (The animals were healthy, Hafler says, and showed no signs of "mad cow disease.") Completing the data collection and analysis will take at least 6 more months, according to Weiner. Meanwhile, David Trentham of Boston's Beth Israel Hospital has begun a preliminary trial of oral collagen in rheumatoid arthritis patients. And Nussenblatt has approval from the Food and Drug Administration to begin a clinical trial of S-antigen feeding in patients with uveitis, which can cause permanent blindness.

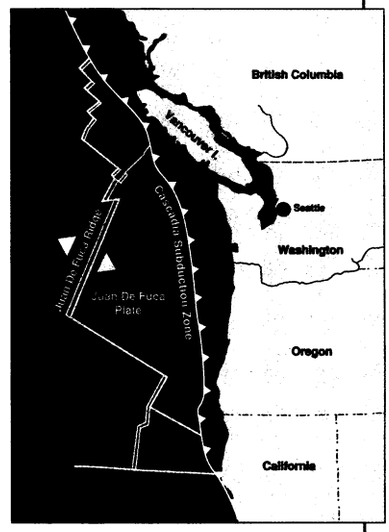
It will be interesting to see over the next few years how antigen feeding will compare with the high-tech modes of therapy, several of which are also moving into clinical trials (*Science*, 20 July 1990, p. 246). The oral approach may have a possible advantage over some of the others, since its success does not depend, as theirs does, on an exact identification of the immune cells causing the autoimmunity. If the oral approach does pan out, says Nussenblatt, it would be "astounding that something as simple as this would work." ■ JEAN MARX

Big Squeeze Points to a Big Quake

Quake country does not end at the Oregon-California border, as is commonly assumed. In fact, the latest evidence from the Pacific Northwest suggests that a big one is in the offing. Seismologists have long known that a huge fault runs off the Oregon and Washington coasts that, in theory at least, could unleash devastating earthquakes like those that ravage Japan. But because none has struck since Europeans arrived 200 years ago, many seismologists had presumed that this fault was harmless. Things took a more ominous turn 4 years ago, when geologists uncovered evidence in marshes and mud flats suggesting that large earthquakes did in fact rock the Northwest in prehistoric times.

Now comes an entirely different sort of disquieting evidence. Geodesists measuring minuscule crustal motions report on page 101 of this issue of *Science* that they have direct proof that the fault in the so-called Cascadia subduction zone is storing energy—energy that will presumably be unleashed in future quakes. The next question, for many seismologists, is whether the coming quake will be merely large or huge.

The new evidence for an impending earthquake in the Northwest comes from stunningly precise measurements of the way drifting tectonic plates are squeezing the coast, literally compressing the earth's crust and forcing the coast upward. Previous measurements had errors almost as large as the squeezing that appeared to be occurring, or else the observations had not run long enough to produce credible results. "What is new is that we have a measurement that isn't marginal," says geophysicist James Savage of the U.S. Geological Survey (USGS) in Menlo Park, who along with colleague Michael Lisowski made the new observations.



Savage and Lisowski had the advantage of using highly precise, laser distance-measuring devices called Geodolites that could rapidly detect the squeezing that is deforming the crust. They measured distances between mountaintop markers in a network laid out in Olympic National Park across Puget Sound from Seattle. Being above the tree line gave their instruments a clear view of other markers in the network, allowing measurements of up to 27 kilometers with a standard error of 6 millimeters.

Savage and Lisowski found that between 1982 and 1990, some markers in the Olympics were squeezed closer together by a few millimeters along a line running North 59° East. At the same time, tide gauges showed the coastline rising a few millimeters per year. This crustal compression and coastal uplift suggest an earthquake is in the works, say Savage and Lisowski. And they lay the blame squarely on the Juan de Fuca plate, which slides toward the North American plate before diving under the continent and into the mantle. If the two plates snagged at the offshore fault where the diving plate scrapes by the other, the Juan de Fuca would squeeze the coast as just observed, they note. A snagged fault would eventually rupture in an earthquake.

There just aren't many ways to interpret this and other evidence, says seismologist William Ellsworth of the USGS in Menlo Park. "A very big earthquake is the most likely explanation. When it comes to public policy, you have to go with that."

The worst case scenario, says Thomas Heaton of the USGS in Pasadena, would be the equivalent of the great 1964 Alaska earthquake (magnitude 9.2), but in an area that houses 10 million people, not a few hundred thousand. The slow rolling of the ground in Seattle and Portland would go on for 3 minutes, with "quite a bit of damage." Even if the 1200 kilometers of fault broke apart section by section in a series of smaller, magnitude 8 quakes, the Northwest would reel for a full minute after each rupture.

On the positive side, there could be a long wait for the next big one. The geologic evidence suggests that earthquakes recur roughly every 500 or 600 years and that the most recent was about 300 years ago. That could, with luck, leave a couple of centuries to prepare for a megaquake in the Northwest. ■ RICHARD A. KERR