Food for Healing

Oral tolerance therapy aims to neutralize autoimmune diseases

By LISA SEACHRIST

Roberta Henderson's daily routine includes a long draft of juice spiked with chicken gristle to ease her arthritic joints. Her more sophisticated friends tell her that this folksy remedy appears antiquated in the face of all the new advances in medical science. But to each of these naysayers, Roberta points out that she experiences far fewer flare-ups of arthritis when taking the concoction, and it certainly does her no harm.

Like her mother before her, Roberta began to experience the agonies of rheumatoid arthritis in her mid-twenties.

Her immune system stopped recognizing the cartilage in her knees, fingers, and hips as part of her own body. It then launched a relentless attack on the cartilage, which is essential for the smooth operation of joints. The result was painful inflammation, loss of motion, and destruction of the joints. Roberta is convinced that only her witches' brew of chicken cartilage keeps her from her mother's fate—confinement to a wheelchair at age 40 because of rheumatoid arthritis.

Roberta Henderson doesn't exist. But such a therapeutic witches' brew is fast becoming more than a flight of fancy. By the year 2000, people may commonly guzzle chicken cartilage proteins for rheumatoid arthritis or snack on cow brain proteins to keep multiple sclerosis at bay. Although reminiscent of 19th-century snake oil medicine, oral tolerance therapy—persuading a person's body to accept foreign proteins by feeding those proteins to the person—may offer a specific, extremely safe way to treat a host of autoimmune diseases. What's more, mounting scientific evidence indicates that this curious reaction has a firm biological basis.

"It's not hocus-pocus," says immunologist Rachel R. Caspi of the National Eye Institute (NEI) in Bethesda, Md. "We can measure responses and confirm our data. This is real."

Animal studies indicate that oral tolerance could be a wildly effective therapy for autoimmune diseases—disorders that occur when the immune system no longer sees a certain tissue as part of one's self but as a foreign invader, then mounts a vicious attack on the offending tissue. Pilot studies of humans, while not establishing that oral tolerance therapy will be effective, have enabled some patients to stop taking conventional immunosuppressive drugs entirely. Those early human tests hint so strongly at a specific therapy with virtually no side effects that the biotech company AutoImmune in Lexington, Mass., is currently sponsoring larger trials.

The phenomenon of oral tolerance isn't new. The response was first described in 1911, when researchers found that they could prevent severe allergic reactions in guinea pigs by feeding them proteins before injecting them with the same proteins. From the 1960s on, scientists continued to demonstrate the effect in animals, using the egg protein ovalbumin as well as feeding red blood cells from sheep to mice before immunizing the mice with the blood cells.

Despite these simple demonstrations that feeding foreign protein to an animal renders it unreactive to the protein, scientists have struggled to explain how oral tolerance works.

"There is a very well developed immune system surrounding the gut that on one level has been ignored by immunology," says neurologist and immunologist Howard L. Weiner of Harvard Medical School in Boston. "That gut immune system has evolved to take in all of the proteins that we eat in our food and not react to them." In fact, foreign proteins that people eat not only fail to trigger adverse immune reactions, they actually suppress immune responses.

Without a fine-tuned, versatile gut immune system, people could suffer extreme immune reactions every time they ate. The presence of any protein not native to the body would become an antigen—material recognized by the immune system—and activate killer T cells, or T1 cells. These specialized white blood cells would then circulate through the blood, attacking related proteins elsewhere in the body.

Instead, the gut immune system appears to have three mechanisms that adapt T cells to deal with foreign proteins. Which of the mechanisms the body employs depends on the amount of foreign protein present in the gut.

When a person has a lot of protein in the gut—for example, after eating a quarter-pound cheeseburger—a process called deletion kills the T cells that would ordinarily react to those proteins. Without those T cells, the body's own proteins are safe. A more modest piece of meat puts the T cells into an inactive phase. And a very tiny nibble of protein will stimulate regulatory T cells, or T2 cells. These cells release the immune system's chemical messengers, or cytokines, which dampen T1 cell activity and lessen inflammation: interleukin-4 (IL-4), IL-10, and transforming growth factor (TGF)-beta.

This ability to neutralize immune responses—particularly inflammation—simply by consuming a target protein has led researchers to study whether oral tolerance could be used to combat autoimmune disorders.

Rheumatoid arthritis, multiple sclerosis (MS), and juvenile diabetes all result from the body seeing its own proteins as antigens—here, autoantigens. The immune system then launches an attack on its own tissues. When that tissue is cartilage, rheumatoid arthritis develops; when it is a brain protein like myelin, the result is MS. No one knows why autoimmune diseases occur, and the only option available to patients at present is to take steroids and immunosuppressive drugs. These drugs suppress the entire immune system and cause serious side effects, including liver and kidney damage, bone loss, and an impaired ability to heal.

In contrast, researchers theorize, oral tolerance therapy would cause T2 cells to release immunosuppressive cytokines only in areas that contain the target protein; in MS, for example, the target would be a specific brain protein. Moreover, a process called bystander suppression causes the cytokines to work on all nearby T1 cells. This additional effect would enable oral tolerance therapy to work even though all the autoantigens involved in a particular disease have not been identified.

"This method is attractive because it allows us to take advantage of a natural route of exposure and a natural system

rather than fighting the body," says Weiner. "And there aren't any toxicities involved in treating people."

In the 1980s, Weiner and his group studied laboratory rats with experimental allergic encephalomyelitis—the rat equivalent of MS. They found that very low doses of myelin basic protein (MBP)—a protein found on the myelin sheath that covers nerves in the brain and spinal cord—suppressed the autoimmune attack on the brain.

These dramatic results in rats led Weiner and colleague David A. Hafler to test the idea in a small group of 30 MS patients. The enigmatic nature of MS leaves its estimated 300,000 sufferers with widely different symptoms. Some people have a single attack and recover, to suffer no more symptoms; others continually decline. But the majority have periods of relative health between attacks, which often result in tremor, balance difficulties, and rigid movements.

The Harvard team tested oral tolerance in patients with a history of relapsing and remitting. Half the group ate low doses of MBP, while the other half, which served as controls, did not. At the end of the study, 12 of the 15 people in the control group had relapsed, while only 6 of the treated group had. "This study provides only a hint of efficacy because it is too small [to establish conclusive results]," says Weiner. "Most importantly, the antigen didn't make them worse."

It was large enough, however, to set the foundation for a double-blind trial sponsored by AutoImmune involving 504 patients from 12 centers in the United States and Canada. The study will monitor relapses among patients and periodically collect magnetic resonance images of their brains to document myelin damage. Because Hafler and Weiner serve as scientific advisors for AutoImmune and have financial stakes in the company, they aren't participating in this larger trial, which is expected to be completed by March 1997.

The theoretical underpinnings of oral tolerance got a boost in July when Hafler and Weiner presented their research results in San Francisco at the Ninth International Congress of Immunology. Comparing the white cells in the blood of 12 MS patients fed MBP daily for 2 years to those found in 10 controls, the researchers found that the treated group had higher concentrations of T cells that secreted TGF-beta and that those cells can control inflammatory responses.

Multiple sclerosis isn't alone in responding to oral tolerance therapy. Caspi has found that low doses of a retinal protein known as retinal S antigen prevent the inflammatory eye disease uveitis in mice. The antigen also stabilizes mice already suffering from uveitis, though "it is always easier to prevent than cure," says Caspi.

Uveitis is responsible for 10 percent of all blindness in adults in the United States. The disease usually strikes between the ages of 20 and 40. Because Caspi's results might benefit uveitis patients, who must take immunosuppressants in order to retain their vision, NEI's Scott Whitcup and Robert Nussenblatt tested retinal S antigen in two patients.

The researchers fed the volunteers very small amounts of retinal S antigen three times a week, then took the patients off their immunosuppressant drugs. Later, the frequency of the antigen dose was lowered to once a week and finally to once a month. Two years later, both patients remain on oral tolerance therapy. One of them takes no other drug, while the other receives extremely low doses of immunosuppressants. "This is an exciting result, given the side effects for the standard therapies," says Whitcup.

Building on this success, Whitcup and Nussenblatt have begun a larger trial. In collaboration with AutoImmune, they are studying 45 patients. Ten will get retinal S antigen, 10 will get a mixture of other retinal proteins, 10 will get both retinal S antigen and the mixture, and 15 will receive a placebo. Should patients relapse, they will be put back on their immunosuppressant medication. Because they can't be sure which antigens cause uveitis, the researchers are testing both retinal S antigen and other proteins to establish the most effective agent, says Whitcup.

Oral tolerance also holds promise for preventing juvenile diabetes, a disease that struck an estimated 674,000 people in the United States in 1993. Matthias von Herrath and Michael Oldstone of the Scripps Research Institute in La Jolla, Calif., are testing oral tolerance in a strain of mice that is susceptible to diabetes after infection with a virus.

The team feeds the mice insulin before the animals develop the disease, in the hopes of preventing destruction of the insulin-producing cells in the pancreas. They treated these mice for 2 months and indeed prevented diabetes—"for good," says von Herrath. Weiner and Hafler had similar success in a strain of mice with a genetic susceptibility to diabetes.

Noel Maclaren of the University of Florida at Gainesville, in collaboration with AutoImmune and Eli Lilly and Co. of Indianapolis, is testing this therapy in clinical trials involving children who have a 20 to 50 percent chance of developing juvenile diabetes within the next 5 years.

Rheumatoid arthritis afflicts over 2 million Americans of all ages. A previous study of oral tolerance in such patients by Harvard Medical School's David Trentham indicated that eating type II collagen—a component of cartilage—significantly reduces the symptoms of this arthritis.

That study spurred a collaboration between Trentham and AutoImmune to study 280 patients at five testing centers. Preliminary results indicate that the lowest dose given was the most effective. "Because of the results, we will have to consider a lower dose in our next trial," says Malcolm Fletcher of AutoImmune.

Because so little is known about how these diseases work—as well the details of oral tolerance—Weiner maintains that "dose is going to be critically important in whether the oral tolerance works."

Once doses are established, Weiner hopes to find ways to prompt stronger tolerance responses. Caspi is already working on enhancing oral tolerance in mice with uveitis. She reported in San Francisco that ineffective doses of retinal S antigen could protect mice if the animals were simultaneously injected with IL-2. "But IL-2 stimulates all T cells, so we will want to look into IL-4 and IL-10, the [T2]-specific cytokines," says Caspi.

In another attempt to enhance oral tolerance, Caroline Whitacre of Ohio State University in Columbus has taken an entirely different tack. She constructed a 20-amino-acid peptide from guinea pig MBP and fed high doses of it to rats predisposed to the rodent analog of MS. None of the rats subsequently developed the disease, but when she fed them the corresponding 20-amino-acid peptide from rat MBP, the animals became sick. The peptides differ by one amino acid. This highlights the sensitivity of the gastrointestinal tract and means that researchers will need to be very exact about which antigens—and how much of them—to use, Whitacre points out.

Not all autoimmune diseases will respond to oral tolerance therapy, says Daniel Drachman of Johns Hopkins Medical Center in Baltimore. Drachman's work in rats susceptible to myasthenia gravis indicates that such an approach may not work against autoimmune diseases in which autoantibodies rather than T cells cause damage.

Drachman used oral tolerance methods to prevent rats from developing myasthenia gravis, but once the rats fell ill, the treatment had little, if any, beneficial effect. "We still may be able to make oral tolerance work on these diseases, but it will take some work," says Drachman, mentioning systemic lupus erythematosus as another autoimmune disease unlikely to respond to oral tolerance therapy.

While Drachman acknowledges that oral tolerance does have an effect, he worries that too much may be expected from the therapy. Weiner agrees that oral tolerance won't get current MS patients out of their wheelchairs, but he notes that "this therapy allows us to deliver pharmacologic doses directly to the tissues that need it. And that's an incredibly attractive concept." □