

NASAL BLOCKADE

Experimental vaccine goes to work where most viruses enter the body. It shows promise not just for cows, but for human health as well.

HOW COULD YOU improve on the immune system? It fights off bacteria and viruses that invade our bodies. How about a new type of vaccine — one that stops dangerous viruses from even entering the body?

Geoffrey Letchworth, a UW-Madison virologist in the Department of Animal Health and Biomedical Sciences, has developed such an experimental vaccine for bovine herpes virus 1 (BHV-1). When sprayed into a cow's nose, the vaccine stimulates the animal's immune system to make antibodies. These antibodies line the cow's nasal passages and block the virus from entering the animal.

The CALS researcher believes the vaccine holds great promise for improving cattle health. BHV-1 infections cause abortions among pregnant cows and lead to shipping fever. These problems cost the U.S. livestock industry hundreds of millions of dollars each year in vaccine and veterinary bills, and in lost production.

Letchworth is equally excited by the implications his findings have for controlling viral diseases in humans. "I think our research here will ultimately benefit human health," he says. "For example, our vaccine is way ahead of vaccines for human herpes viruses." Among the family of human herpes viruses are the viruses that cause cold sores, chicken pox, shingles, roseola, mononucleosis, Kaposi's sarcoma and cytomegalovirus (CMV) infections.

Although there is encouraging new evidence that drugs might eliminate the Human Immunodeficiency Virus from individuals with AIDS, animals and humans do not eliminate herpes viruses once they have become infected. The immune system suppresses these viruses, which hide in the body and can become active again during periods of stress. Current herpes vaccines don't keep out viruses either.

Letchworth's approach builds on scientists' growing understanding of the role mucous membranes play in viral infections.

"Most viruses enter animals and people through mucous membranes," Letchworth says. "A few viruses, such as rabies, get into the body other ways. But most cross the mucous membranes around the eyes, or those that line



The subject doesn't appreciate it, but the vaccine goes where it's needed. UW-Madison virologist Geoffrey Letchworth (left), animal caretaker David Starks and grad student Xiaoping Zhu apply an experimental vaccine via nose spray. The vaccine stimulates production of antibodies that line the cow's nasal passages and block the virus from entering the animal.

breathing passages, the gastrointestinal tract or reproductive tract."

However, most vaccines are injected into muscle where they are supposed to mimic an actual infection, priming the immune system so it responds quickly when the real virus enters an animal or person.

"When you inject a vaccine into a muscle, the immune system in a lymph node nearby makes antibodies that circulate in the blood and lymph systems," Letchworth says. "But you get a much different response by placing the same antigen on mucosa. That response stimulates a completely different part of the immune system, which appears to protect the body's surfaces. Our idea was to stimulate that part of the immune system."

Letchworth and research assistant Xiaoping Zhu tested the vaccine on 20 cattle from a herpes-free herd. After vaccinating the animals, the scientists challenged each cow with ten million units of BHV-1.

"That's an extraordinarily large dose. That one dose contains enough virus to infect every cow in Wisconsin," Letchworth says. "We wanted the challenge dose to be great enough to infect some animals so we could find the lim-

its of protection. Despite that huge dose, 70 percent of the cows remained free of the virus."

Letchworth also tried the conventional approach in which he injected the vaccine into muscle. When he challenged those cattle with the virus, the vaccine did not protect them. They became infected with BHV-1 and shed it when stressed with steroids.

All the common livestock animals — pigs, horses, chickens, sheep, cattle — have several herpes species that infect only them and closely related wild relatives, according to Letchworth. BHV-1 is the most serious of four herpes species that infect cattle. BHV-1 infections produce a disease cattlemen call IBR (infectious bovine rhinotracheitis). Cattle with IBR initially develop cold-like symptoms. If a cow is pregnant when she becomes infected, she often loses the calf 30 days later. Such abortions are a significant problem for dairy farmers.

Cattle with IBR develop shipping fever, a pneumonia-like disease, when the viral infection is accompanied by an infection with *Pasteurella* bacteria. Shipping fever, a major problem for beef cattle in large Western feed lots, is often fatal.

To control IBR, farmers and ranchers need to immunize cattle soon after they are born. Because the current vaccines protect for about a year, animals must be vaccinated again annually. The vaccines for IBR are widely used to decrease the shedding of virus from animals and thereby protect other cattle from infected individuals.

Part of Letchworth's goal is a vaccine that is directly available to farmers and easy to administer. "Cows don't like to have things sprayed into their noses," he says, "so we want to make lots of the protein cheaply and devise ways that are easy for farmers to use." Letchworth envisions a modified feeder; when an animal sticks its head in to feed, a dose of the vaccine would be sprayed into the air above the feed.

The UW-Madison virologist doesn't know how long the vaccine will protect cattle. He thinks such a vaccine would be short-lived, probably less than a year. But, he says, animals could be vaccinated over and over fairly easily.

Letchworth has received a U.S. patent on the use of herpes viral glycoproteins for preventing infection. His research has been supported by USDA competitive grants and a Shaw Scholarship.

GEORGE GALLEPP

FEMALE FISH ARE FAVORED. STERILE FISH MAY BE EVEN BETTER.

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To come up with a method to produce sterile fish, Malison and his group have been delving into the world of polyploidy. Polyploid organisms have more chromosome sets than is usual for their species. Fish are normally diploid, that is, they have two chromosome sets. Malison's team set out to produce triploids, fish that have three chromosome sets and are typically unable to reproduce.

To induce polyploidy in perch and walleye, the researchers apply either heat shock or intense pressure to fish

eggs to create tetraploids, fish with four chromosome sets, and then mate them with the normal diploids. Assuming tetraploids will be fertile, pairing them with diploids should produce triploid fish.

The methods used to create tetraploids are similar to those used to produce triploids, except that the heat or pressure shocks are applied at a later developmental stage. Malison's group has produced several hundred perch that have four chromosome sets. They are now waiting for them to mature, a

long process, because the tetraploids seem slow-growing and weak. Malison says this is probably due to the shock they received rather than because of their altered genetic structure. If successful, the tetraploid/diploid pairing will result in triploid perch that never received heat or pressure shocks. The technique should eliminate the drawbacks produced by the direct shock method.

MARIE MARTINELL