(HBsAg) may provoke an autoimmune attack on a similar protein in the nerves or other tissues of a genetically susceptible group of vaccine recipients. This "molecular mimicry" scenario is at least plausible.

In this issue of *Science*, for example, researchers report evidence that the Lyme disease organism can trigger arthritis in this way (see pp. 631 and 703). And other molecular biologists have published papers arguing that the herpesvirus triggers MS and an eye disease called stromal keratitis through molecular mimicry. Still others think the Coxsackie virus induces diabetes through such mimicry. To be sure, these scientists have laboratory results to support their proposals—something Dunbar lacks, although she plans to undertake such studies in collaboration with an immunogeneticist and a hepatitis virus expert at the University of Oklahoma. A grant application they submitted to the National Institutes of Health (NIH) has now been turned down twice, however. Dunbar says she may even try to pay for the research herself.

Other vaccine experts are skeptical of the molecular mimicry thesis. Neal Halsey, a leader of the American Pediatric Association and director of the vaccine safety center at Johns Hopkins University, thinks those who attribute risk to the vaccine have not begun to make a case. He says, "I am not finding any scientific evidence that there are any cross-reacting antigens" in the vaccine that might trigger an attack on nerve tissue. Halsey also points out that infection by the natural hepatitis B virus has not been identified as a risk factor for MS; why, he asks, would a fragment of virus protein used in a vaccine be riskier? And Kane notes that although the prevalence of MS is highest among people in northern Europe and North America, hepatitis B rates are highest near the equator. One would expect an overlap, he says, if the virus and MS were biologically linked.

Still, claims that the hepatitis B vaccine triggers autoimmune disease caused one vaccine manufacturer—Merck & Co. of Whitehouse Station, New Jersey—to sponsor a day-long review of the available data in Atlanta on 21 March 1997. When the session ended, the participants, including Kane, Chen, an NIH expert in molecular mimicry, Army researchers, and scientists from the chief vaccine makers—Merck, SmithKline Beecham of Philadelphia, and Pasteur Mérieux Connaught (PMC) of Lyon, France—agreed that the available data were very sketchy. They found no association between hepatitis B vaccine and the onset or exacerbation of MS. But they concluded, according to the minutes of the meeting, that "epidemiologic studies should be conducted because of public concern."

At least three studies have been launched, according to Robert Sharrar, a Merck medical officer. Merck is spending about $260,000 to help obtain hepatitis B immunization data from an ongoing, independent study of nurses' health in Boston. PMC is helping to fund a study of immunization run by MS clinics in France. And Chen confirms that CDC is collecting data from four health maintenance organizations on the West Coast for a study of MS and hepatitis vaccination. Sharrar says the Boston study could yield data next summer. The CDC project may take longer.

Although public health officials are confident that the hepatitis B vaccine is safe, they know they are likely to face more claims of vaccine-induced injuries in the future. This infuriates some proponents of universal immunization. "This vaccine prevents cancer," says Halsey. "For me, it is incredible that people are not taking into account the potential harm to public health they are doing" by raising an alarm.

Chen is more philosophical. Now that millions of people are receiving hepatitis B shots each year, he says, many will blame it for any misfortunes that follow. "It's human nature," he says, to attribute cause to almost anything that precedes a tragedy. **–ELIOT MARSHALL**

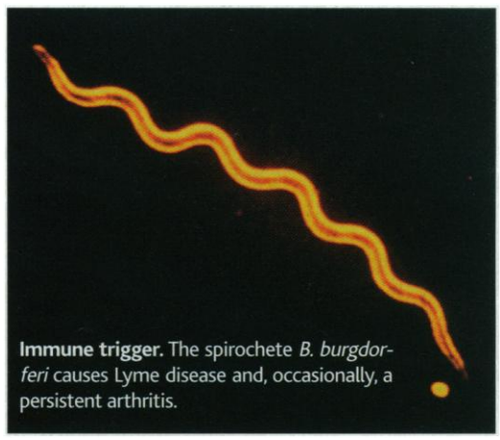
IMMUNOLOGY

Possible Cause Found for Lyme Arthritis

The inflammatory attack on joint tissue may be triggered by a protein carried by the Lyme disease organism

For many unlucky Lyme disease sufferers, the disease has a painful way of lingering. Weeks or months after the tick bite that transmits the disease-causing bacterium, some patients develop arthritis. Usually, the condition disappears following antibiotic treatments. But in roughly 10% of the patients, it persists after the infection has vanished. This has been a major mystery. As rheumatologist Brian Kotzin of the University of Colorado Health Sciences Center in Denver asks: "Why this perpetual response in the joint if the bug is not there any more?" The answer, researchers now say, is an immune response that goes awry.

On page 703, Allen C. Steere of the New England Medical Center in Boston, Brigitte T. Huber of Tufts University School of Medicine, and their colleagues report the discovery of a striking resemblance between a protein found on the outer surface of the Lyme disease organism—the spirochete *Borrelia burgdorferi*—and a protein carried on human cells. This suggests that some people develop the persistent arthritislike condition because the infection triggers immune cells that attack both the spirochete protein and their own normal cellular protein.



CHARLES W. STRATTON / VISUALS UNLIMITED

Immune trigger. The spirochete *B. burgdorferi* causes Lyme disease and, occasionally, a persistent arthritis.

Immunologists are intrigued by the finding because it may be one of the few cases in which both the precise trigger for an autoimmune attack and its target in the body have been uncovered. "This is perhaps a unique opportunity to work front to back," from the trigger to the misplaced immune response, says rheumatologist Leonard Sigal of the Robert Wood Johnson Medical Center in New Brunswick, New Jersey. As such, it could help researchers design new drugs or vaccines for Lyme disease arthritis.

Perhaps even more important, the discovery could have implications for efforts to develop vaccines against Lyme disease, of which there are about 16,000 new cases every year. Just last week, *The New England Journal of Medicine* published the results of two large-scale clinical trials of Lyme disease vaccines. Both were very effective, but both are made from the very same spirochete protein linked to autoimmune arthritis by the Steere and Huber team.

In theory, the protein might provoke autoimmunity in some people who receive the vaccines, as some patients and researchers now claim the hepatitis B vaccine is doing (see story on p. 630). "This is an issue

of concern," says Steere, who was also a principal investigator on one of the vaccine trials. Indeed, he notes, arthritis did develop in several subjects who received the vaccine, although a number of the controls also became arthritic. "Ongoing surveillance will be important" to detect any problems, he adds.

The path to the current finding began about 10 years ago. Immunologists know that some people are genetically predisposed to autoimmunity because of natural variations in their so-called HLA molecules, which reside on certain immune cells and help determine to which antigens a person responds. And in 1989, the Steere team found that the patients who get persistent Lyme-related arthritis very often carry a particular HLA variant designated *DRB1*0401*. Because that same variant is associated with rheumatoid arthritis, an autoimmune disease, it seemed that Lyme disease arthritis might itself result from an autoimmune attack, possibly triggered by a *B. burgdorferi* antigen that resembles some component of human joint tissue.

So, Steere and his colleagues looked for antigens on the pathogen that *HLA-DRB1*0401* might recognize. And in 1994, they found one that might fit the bill: a *B. burgdorferi* protein called OspA (for outer surface protein A) that was frequently recognized by the T type of immune cells from treatment-resistant patients but recognized only uncommonly by T cells from those whose arthritis responded to treatment. OspA had also become the primary component of the Lyme disease vaccine because it provided a protective antibody response in animals injected with it.

Steere's group then joined forces with immunogeneticist Huber to look for human proteins that might resemble OspA. Using a computer algorithm based on a previous lab analysis of DRB1*0401's peptide-binding abilities, they showed that DRB1*0401 binds to a particular nine–amino acid segment of OspA when it triggers an immune response. Then, the scientists searched a database looking for human proteins that contain the same sequence and might therefore be the target of an autoimmune attack initiated by OspA. They turned up one candidate, a protein called hLFA-1, found on blood and other cells.

When the researchers studied T cells from 11 patients with treatment-resistant Lyme arthritis, they found that nine of them carried T cells that respond strongly to the key sections of both OspA and hLFA-1. T cells taken from controls with other forms of arthritis did not show those responses. These findings suggest, Steere says, that T cells originally triggered to recognize OspA go on to attack the unfortunately similar part of hLFA-1 found on the patients' own cells.

Steere and Huber are quick to admit, however, that the evidence for this scenario is circumstantial. One worry is that they couldn't find hLFA-1–reactive T cells in all 11 patients, although Kotzin says that may just be because T cells from joint fluid can be hard to study. "That they are able to demonstrate such a specific response from these T cells is really remarkable," he adds.

But if that specific response to hLFA-1 causes the arthritis, asks immunologist Kai Wucherpfennig of the Dana-Farber Cancer Institute in Boston, why is the inflammation confined to the joints, while hLFA-1 is found on cells all over the body? One explanation: T cells naturally have hLFA-1 on their surfaces and therefore carry it along when they move into joints to combat *B. burgdorferi* infections. This may exacerbate immune-cell responses to hLFA-1, resulting in a vicious cycle in which the joints become permanently inflamed. Nonetheless, Wucherpfennig wonders whether "there may be other important targets that have not yet been identified."

Researchers might be able to settle these issues if they could recreate treatment-resistant, Lyme-related arthritis in an animal such as the mouse. So far, however, they haven't been successful, perhaps because mice have a different form of LFA-1. "This is an initial observation," says Steere. "Now, one sets forth on the next phase of the journey."

–STEVEN DICKMAN

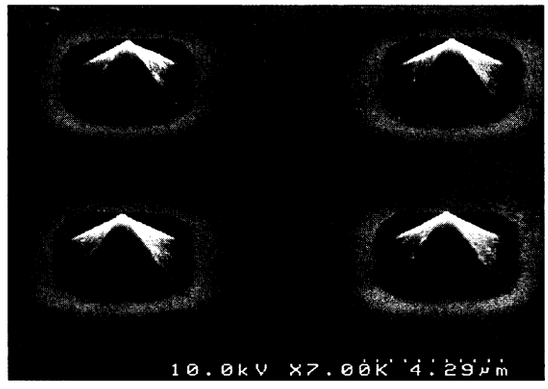
Steven Dickman is a writer in Cambridge, Massachusetts.

TECHNOLOGY

Field Emitters Finding Home in Electronics

New materials promise smaller, more efficient way to deliver electrons to flat-panel displays, cameras, and microscopes

TSUKUBA, JAPAN—The big vacuum tubes and copper wiring that filled the backs of early televisions have long since been replaced by tiny semiconductor chips and printed circuit boards. The one holdout against miniaturization is the cathode ray tube (CRT), which retains all the bulk and inefficiency of 50 years ago. Various flat-panel display technologies have emerged, but none matches the brightness and resolution of the CRT, in which a heated filament spews a stream of electrons that light up phosphors on the image screen. But time may finally be catching up with the CRT.



J. DAVIDSON, W. P. KANG/VANDERBILT UNIV.

So long, silicon. These diamond tips (magnified 7000 times) form part of an emitter array developed by researchers at Vanderbilt University.

A recent meeting here* highlighted advances in a technology that uses an electric field rather than heat to wrest electrons from an emitter material. A key step forward in this technology, called field emission, is the use of more durable materials that promise slimmer, more energy-efficient, and portable displays for personal computers. Perhaps more significantly, researchers are also applying field-emission technology to microscopes, image sensors, and other devices that have traditionally used electron guns, like those in CRTs, as electron sources. New uses for field emitters "have been popping up like mushrooms," says Chris Holland, a field-emission specialist at SRI International in Menlo Park, California. That activity, he says, is a good indication of how quickly the field is maturing.

Field emission is not a new idea, either. But the pointlike cathodes—traditionally made of silicon or tungsten—have tended to break down quickly in the powerful electric fields. Researchers have long had their eye on diamond film as a cathode material, but it has proven tough to fabricate into the sharply pointed shapes needed for electron emission.

* The Second International Vacuum Electron Sources Conference, Tsukuba, Japan, 7–10 July.