Critics blame the widely used vaccine for many ills, citing anecdotes and a theory of molecular mimicry, similar to one proposed for Lyme disease arthritis—but scant data

A Shadow Falls on Hepatitis B Vaccination Effort

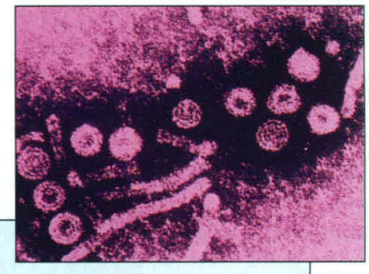
Hepatitis B seems to be the perfect target for a vaccine. Spreading quietly through blood contact, sex, and birth, the virus currently infects 350 million people worldwide, according to the World Health Organization (WHO)—mostly without producing symptoms. But in a fraction of cases, those infections lead to liver failure or liver cancer, deadly complications that each year kill an estimated 1 million people around the world and about 4000 in the United States.

In the 1980s, public health officials in Europe and the United States sought to reduce this toll by mandating the immunization of adults in high-risk categories, such as healthcare workers, and, in 1991, all newborns. But now a shadow has fallen across the vaccination campaign.

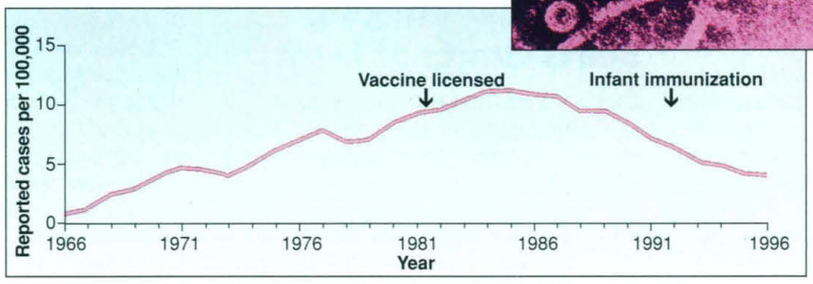
A growing number of those who have received the vaccine shots—although just a tiny fraction of the 200 million immunized—claim to have experienced serious adverse effects. Their medical complaints cover a spectrum of autoimmune and nervous system disorders, including rheumatoid arthritis, optic neuritis, and neurodegenerative illnesses that resemble multiple sclerosis (MS). Now, some researchers are proposing that the vaccine tricks recipients' immune systems into attacking their own tissues. And a legal onslaught may be beginning.

Already, several groups are seeking compensation from governments and manufacturers or demanding that mandatory vaccination be stopped. On 17 July, for example, an alliance of antivaccine activists in France filed a lawsuit in Paris against the national government, accusing it of understating the vaccine's risks and exaggerating the benefits for the average person. The attorneys, who seek a criminal inquiry, claim to represent 15,000 people. And in the United States, several East Coast lawyers representing clients with hepatitis vaccine claims held a summit near Washington, D.C., in July to discuss strategy. ABC's *20/20* program, meanwhile, is filming a documentary on hepatitis vaccine risks that may be aired this fall.

Vaccine safety officials interviewed by *Science* say they have seen no evidence that autoimmune diseases like MS are appearing at a higher rate among vaccinated people. Indeed, a French government study last year found that vaccinated people were less likely to have MS. "These fears [of the hepatitis B vaccine] are quite unfounded," according to Mark Kane, director of the hepatitis vaccine program at the World Health Organization. But he and other health officials worry that scary publicity about the vaccine could interfere with the drive for immunization.



VISUALS UNLIMITED



SOURCE: CDC

Hidden threat. The hepatitis B virus *(inset)* infects many more people than U.S. case counts indicate, but the total is in decline.

They also worry that they may get caught in what Robert Chen, vaccine safety chief at the Centers for Disease Control and Prevention (CDC) in Atlanta, refers to as a Catch-22. Chen and his colleagues say they are taking the claims of injury seriously. Epidemiological studies to see if there is a link between hepatitis B vaccination and MS—the most publicized concern—have already begun, and some data may be available next year. But, perhaps mindful of a similar controversy over whether silicone breast implants cause autoimmune diseases, Chen and his colleagues fear that any study—even if results prove negative—will add legitimacy to the claims. According to Chen, who commissioned one of the new studies, "The folks who oppose the vaccine will say … that just because we are looking at it, that must mean there is an association" between the vaccine and the illnesses.

Concern about the vaccine appeared early in France and now seems to have gained the most attention there. Physician Philippe Jacubowicz, who heads an organization in Paris called REVAHB, has collected data on more than 600 cases of illnesses, many with MS-like symptoms, in people who had received the hepatitis B vaccine. In addition, patient advocacy groups in Britain and Canada have studied more than 100 cases each, as has an outspoken U.S. accuser of the hepatitis B vaccine, Bonnie Dunbar, a molecular biologist at Baylor College of Medicine in Houston.

A developer of contraceptive vaccines herself, Dunbar is a forceful critic. And she is motivated by personal experience: Her brother developed immune problems that she believes were triggered by the hepatitis B shots he had to get when he became a health care worker. Dunbar says that when she began investigating, she found that other medical colleagues had experienced or knew about such reactions. One nurse, for example, attributed a dozen cases of MS to vaccination.

To support her case, Dunbar is culling data from a list of more than 20,000 reports of miscellaneous adverse reactions to hepatitis B vaccination, filed with the Food and Drug Administration's (FDA's) Vaccine Adverse Event Reporting System (VAERS). FDA officials themselves have so far identified 111 MS cases in VAERS that appeared after vaccination, but they say a review of the medical records from these cases has turned up no evidence that they were actually caused by the vaccine.

Dunbar thinks the FDA may be overlooking a possible biological mechanism. To explain the apparent bad reactions, she postulates that a hepatitis B surface protein used as an antigen in the recombinant vaccine

(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 daylong 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**

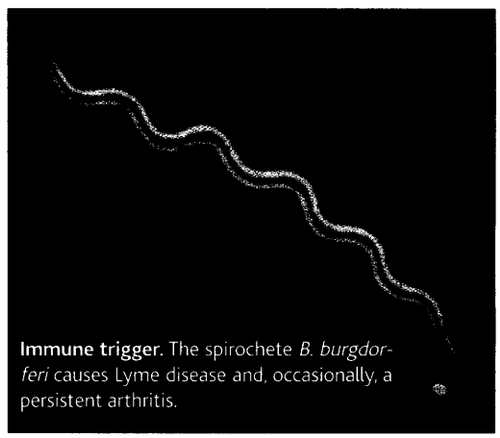
IMMUNOLOGY

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