PUBLIC HEALTH

Aluminum Is Put on Trial as A Vaccine Booster

Complaints about vaccine safety and debate over a mysterious muscle ailment have prompted researchers to take a fresh look at the use of aluminum

SAN JUAN, PUERTO RICO—A few years ago, Romain Gherardi, a pathologist at Henri Mondor University in Céteil, France, noticed something unusual in tissues taken from a few hospital patients who complained of sore muscles and fatigue. Muscle biopsies from the patients' upper arms contained unusual aggregations of macrophages, the body's multipurpose cleaning cells. Worried that the finding heralded the arrival of a new disease, Gherardi and his colleagues published an article in the August 1998 issue of *The Lancet* describing the condition as Macrophagic Myofasciitis (MMF), "a new inflammatory muscle disorder of unknown origin."

Gherardi has since developed a controversial theory about what causes the rare disorder: It is aluminum, he believes, the same ingredient that has long been added to many vaccines to give them a more powerful immunological punch. The idea has propelled Gherardi into the middle of a volatile public debate over the safety of vaccines. The disputes have run from worries over the use of mercury as a preservative to allegations that vaccines contribute to allergies and autism (*Science*, 31 July 1998, p. 630 and 14 April, p. 241). And this month, as some 70 scientists gathered here* for 2 days of often vigorous discussion of Gherardi's findings, a larger question hung over the gathering: Will aluminum be the next battleground in the vaccine wars? "The vaccine community is on edge about any perceived safety issue, because it has been a very difficult past few years," says physician Michael Gerber of the National Institute of Allergy and Infectious Diseases in Bethesda, Maryland.

Unlikely suspect. Aluminum would seem to be an unlikely source of concern. For nearly 70 years, vaccinemakers have used three aluminum salts—alum, aluminum hydroxide, and aluminum phosphate—to add oomph to many vaccines, including widely used formulations for diphtheria, hepatitis B, and tetanus (see table). These adjuvants, or helper chemicals, cause the body's immune system to react earlier, more potently, and more persistently to the antigen contained in the vaccine. Despite aluminum's potency, there are relatively few reports of adverse reactions, and those are usually limited to temporary muscle soreness or swelling at the injection site. "Aluminum vaccines have an excellent track record," says vaccine expert C. John Clements of the World Health Organization in Geneva, which each year supplies vaccines for millions of children.

COMMON U.S. VACCINES WITH ALUMINUM

Vaccine	Manufacturer	Dose (mg)*
DTAP Infanrix	SmithKline Beecham (SKB)	3.1
DTAP Certiv	North American Vaccine	2.5
DTAP Acel-Immune	Lederle	1.2
DTAP Tripedia	Pasteur Mérieux Connaught	0.9
DTP	Bioport	2.0
DTP	Connaught	0.5
DTP-HIB Tetramune	Lederle	3.4
HepBHIB Comvax	Merck	0.7
HepB–Recombivax B	Merck	0.7
HepB–Engerix B	SKB	0.8
Tetanus	Lederle	2.9
Tetanus	Wyeth	5.1
Tetanus	SSVI	5.1

Source: FDA

* Total dose over complete series.

Given that track record, Gherardi was surprised when a colleague informed him in October 1998 that the macrophages in his tissue samples were filled with aluminum. "We did not believe it," Gherardi recalls. At the meeting, however, researchers agreed that it is aluminum—and that it comes from vaccines. They also agree that measurable quantities of aluminum can remain at the injection site for surprisingly long periods—up to 8 years in one of the French patients. But most vaccine researchers remain highly skeptical that the metal is the cause of nearly 150 cases of MMF found to date.

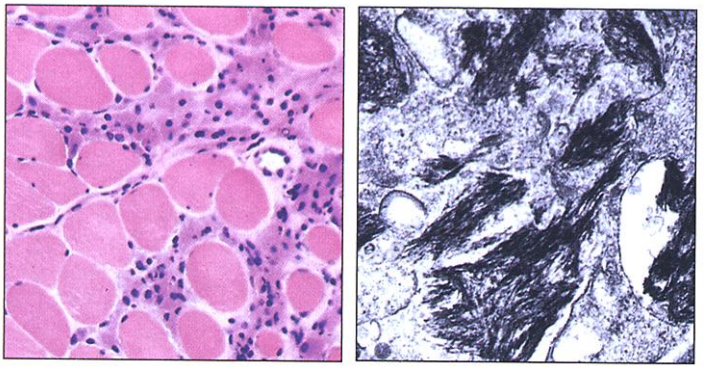
Several conferees questioned whether MMF is actually a distinct disease. "I didn't come away convinced that this is a new disorder," says Neal Halsey, head of the Institute for Vaccine Safety at The Johns Hopkins University in Baltimore, Maryland. It could be "an epidemic of recognition," notes professor of medicine Theodore Eickhoff of the University of Colorado, Denver, in which doctors ascribe previously unnamed symptoms to a newly described disorder. Still others wonder whether the epidemiological association between MMF and the muscle ailment is a byproduct of tissue sampling practices in France, where doctors routinely take tissue from the upper arm, often the site of vaccinations, instead of the leg or other muscles.

Finally, many scientists say that the French results are flawed by a lack of control groups. In particular, the existing studies do not show how many vaccinated people are carrying the MMF aluminum deposits but exhibit no symptoms. As a result, "it would be premature and dangerous to ascribe this condition to vaccines," says Vito Caserta of the U.S. government's Division of Vaccine Injury Compensation in Rockville, Maryland.

Gherardi agrees that the MMF-aluminum association is far from proven. But he is confident that the symptoms he has described can be distinguished from similar ailments. What's more, he asserts, "there are MMF patients in the U.S. [and other nations who] are not detected due to differing biopsy practices." The spate of recent cases, he adds, might be explained by France's decision several years ago to vaccinate nearly 40 million adults against hepatitis B. Gherardi insists he is just as eager as his critics to do a controlled study to look for MMF lesions in people without symptoms, calling it "a critical piece of information." Although French regulations make it difficult for researchers to take muscle biopsies from a control group of healthy patients, he says, researchers are moving ahead with a range of other human and animal studies to ferret out more detail.

Answers in cadavers. To prepare to answer any potential public concerns, the U.S. government is initiating its own aluminum research, says Martin Myers, acting director of the National Vaccine Planning Office, which organized the meeting and helps coordinate vaccine-related work across the federal government. One study

* Workshop on Aluminum in Vaccines, 11 to 12 May, San Juan.



Telltale sign? A French study says aluminum-filled macrophage cells (blue, left, and close-up, right) could be linked to a rare muscle ailment.

might help settle the MMF debate by examining tissue samples taken from cadavers. Other high-priority projects, he says, may include setting guidelines for the amount of aluminum that should be allowed in injectable vaccines (the current standard applies to oral vaccines), collecting more data on how young children process aluminum, and examining whether changing the way some aluminum-adjuvated vaccines are injected might further reduce the risk of adverse reactions. Also possible are clinical studies to evaluate the differences between the three kinds of aluminum adjuvants and the role that adjuvants alone play in causing swelling and muscle pain.

Ironically, some of the new studies may get a boost from a controversy surrounding the U.S. military's anthrax vaccine, which includes aluminum. Last year, after some soldiers and pilots refused to take the vaccine as ordered by the Defense Department, Congress called for a large-scale clinical trial to answer safety questions. That trial, due to begin later this year, may now be designed to answer questions about aluminum adjuvants, too. Sparked by the French research, vaccine manufacturers are also jumping into the act. SmithKline Beecham researchers, for instance, are in the midst of large-scale animal studies of aluminum's biological impacts, as well as surveys designed to detect adverse reactions among patients.

Vaccine researchers hope the new data will help avoid what several call "Thimerosal II." Thimerosal, a mercury compound used to prevent vaccines from becoming contaminated by bacteria or fungi, is now scheduled for elimination from several common vaccines after federal officials and some public interest groups raised questions about its safety. During debate over the last few years, however, many vaccine researchers felt hamstrung by a lack of data on everything from mercury's interaction with other vaccine compounds to acceptable doses for infants. Indeed, when the aluminum issue arose, "I had a sense of déjà vu," says Alison Mawle, a researcher with the Centers for Disease Control and Prevention in Atlanta, Georgia. "There are huge gaps in what we know about the toxicity of aluminum."

For the moment, researchers and public health officials, including Gherardi, see no reason to remove aluminum from vaccines. But they may examine the feasibility of reducing the amount used in some vaccines—just in case. Scientists say that it's not clear, for instance, that the adjuvant is necessary to ensure the effectiveness of booster shots, which are administered after the immune system has already reacted to the initial dose. However, manufacturers say any effort to replace aluminum with another adjuvant would be costly and complicated. Regulatory and manufacturing requirements, for instance, would make it "a nightmare" to create different formulas for an initial vaccine and its booster, says Nathalie Garcon-Johnson of SmithKline Beecham Biologicals in Rixensart, Belgium.

Most researchers left the San Juan meeting feeling reassured about aluminum's safety. But some government officials remain worried that the subject could blow up into a legal and political battle. Web sites published by some anti-immunization groups, for instance, already finger aluminum as a cause for concern. In light of such sentiment, Caserta urged a panel drafting the workshop's summary statement on MMF to tread cautiously. "We have to be very careful with our ideas," he says. "The courts don't know how to deal with [uncertainty about] causality."

–DAVID MALAKOFF

EUROPEAN SCIENCE

A Blow to Austria's Scientific Revival

Since the Nazi occupation tore apart its scientific community, Austria has revived many fields. Now budget cuts threaten the momentum

VIENNA—Less than a century ago, this cultural bastion on the Danube was a vibrant scientific capital, nourishing great minds such as theoretical physicist Erwin Schrödinger and psychoanalyst Sigmund Freud. But a mass exodus in the late 1930s crippled Austria's intellectual dynamo, and the impoverishment deepened after much of the city was destroyed during World War II. Slowed by stingy postwar government support, the seeds of good science did not take root again until the late 1960s, giving rise to centers such as Vienna's Atom Institute and, later, Anton Zeilinger's quantum teleportation labs in Innsbruck and Vienna (see sidebar on p. 1327). And although Austria still lags many other European nations in broad science indicators, a government pledge last year to pour more money into research fueled hopes of a true scientific resurgence. "In the last few years, you got the feeling that science was improving rapidly here," says Helmut Ruis, who heads the University of Vienna's Institute of Biochemistry and Molecular Cell Biology. But Austria's budding scientific renaissance is suddenly in jeopardy.

Glorious past. Schrödinger was part of Austria's vibrant prewar scientific community.

Last week, the Austrian Parliament approved an austere science budget that slashes support for the Austrian Science Fund (FWF)—the country's basic research granting agency—by 26% and savages spending on laboratory upgrades by nearly two-thirds. "These budget cuts—coming at a time when Austrian science has been on the upswing—threaten to endanger basic research here," says solid state physicist Peter Skalicky, rector of the Technical University of Vienna. And the embattled Austrian government's recent contretemps with many of its European Union partners could doom a major project on the drawing board, the AUSTRON neutron

CREDITS: (TOP TO BOTTOM) R. K. GHERARDI; CORBIS/HULTON-DEUTSCH COLLECTION