Phage in Live Virus Vaccines: Are They Harmful to People?

Almost 2 years ago, scientists at the Bureau of Biologics of the Food and Drug Administration (FDA) reported that all live virus vaccines are grossly contaminated with phage (viruses that infect bacteria). This finding presented a problem since federal regulations forbade extraneous material in vaccines, and no one knew whether phage are harmful to human beings or whether they could be removed from vaccines. The temporary solution was to amend the regulations so as to permit phage in vaccines. Now the FDA plans to propose regulations, which may go into effect as early as 1 July of this year, that should eliminate phage from human vaccines.

Grumbling researchers at pharmaceutical companies that manufacture live virus vaccines, such as Lederle, Dow, and Merck Sharp & Dohme, are aware of the proposed new federal regulations and are preparing for them. However, they feel that hypothetical dangers from phage in vaccines have been greatly exaggerated. Some biologists disagree, but, as so often happens when there are reasons to expect that a substance is harmful to human beings, biologists who are worried about the effects of phage in vaccines do not know enough about the molecular basis of human disease to convince others that their fears are justified. In the middle of this confrontation between a small group of biologists and representatives of drug companies are scientists at the FDA's Bureau of Biologics, who had to decide whether phage should be eliminated from human vaccines and, if so, how.

Before they could make any decisions on how to deal with phage in vaccines, investigators at the bureau had to find out how phage got into the vaccines. This turned out to be fairly straightforward and, according to John Petricciani, who is head of the bureau, they are now nearly certain that phage are introduced into vaccines when viruses for the vaccines are grown in tissue culture.

Phage have been found in fetal bovine serum, which contains "growth factors" necessary for the propagation of cells in tissue culture. These cells are used to grow human viruses for the vaccines. When fetal bovine serum is collected at a slaughterhouse, it becomes contaminated with large numbers of bacteria—as many as 10^8 bacteria per milliliter of serum, according to Petricciani. The serum is then filtered to remove bacteria, but the phages pass through the filter. To eliminate these phage, vaccine producers will have to use only sterilely collected serum.

But getting sterile serum is difficult and expensive. Serum distributors, who estimate that such fetal bovine serum could cost twice as much as other serums (its price could increase from about $60 to about $120 per liter), complain that federal regulations hinder all attempts to prevent bacterial contamination of serum because it must be collected in a room of a slaughterhouse where fetuses, along with all other inedible parts of animals, are thrown. The room is dirty and, according to one spokesman, "one minute you have nothing to do and the next minute you are literally knee deep in fetuses." The least the Department of Agriculture (the agency that supervises slaughtering procedures) could do, a spokesman for Microbiological Associates, which supplies serum, complains is give them a clean room in which to collect serum.

Known Effects of Phage

Although the Bureau of Biologics is acting quickly, for a federal agency, some biologists, the most vocal of whom is Carl Merrill of the National Institute for Mental Health in Bethesda, Maryland, fear that it is not acting quickly enough to end the contamination of human vaccines. They are convinced that three known effects of phage on humans or mammalian cells are sufficiently ominous to indicate that no more phage-contaminated vaccines should be sold.

The first effect of phage on human beings is indirect: certain human diseases, such as scarlet fever and diphtheria, are caused by bacteria that are infected with phage and cause them to produce a toxin. A person could possibly take an oral polio virus vaccine, for example, that was contaminated with phage that infects corynebacteria and thus causes them to secrete diphtheria toxin. If the intestinal bacteria included susceptible corynebacteria, that person could contract diphtheria.

A second effect of phage is that they can transmit genes to human cells in tissue culture. Phage can be made to carry a specific gene that human cells lack. When exposed to such phage, the human cells will begin to synthesize the protein coded by that gene. Merrill, who first described this phenomenon, believes that it may be possible for phage to transmit genes to human cells and to thereby cause cancer or degenerative diseases in human beings.

A third effect of phage on mammalian cells—recently reported by Paul Ts'o and John Leavitt of Johns Hopkins University in Baltimore, Maryland—is that certain phages can replicate in hamster cells in tissue culture. Although the implications of this finding are as yet unknown, it leads Merrill to believe that phages may routinely infect human cells and cause diseases.

More conclusive evidence that contamination of live virus vaccines with phage is harmful would be epidemiological evidence; but, unfortunately, such evidence has not and perhaps cannot be obtained. Although millions of people have received live virus vaccines for polio, measles, mumps, and German measles, few countries have kept medical records that could be examined to determine whether the introduction of vaccines is correlated with an increased incidence of either infectious diseases or degenerative (or other) disorders. Even in cases in which a vaccine is shown to be associated with such deleterious effects, no records exist of specific phage contaminants of specific lots of vaccine, according to Petricciani. And, as Merrill stresses, no one yet knows either the extent of phage contamination or the identity of all of the phage contaminants of vaccines.

Representatives of serum processing and pharmaceutical firms tend to disagree with the biologists who worry about the potential harm associated with phages in vaccines. A spokesman for Merck Sharp & Dohme points out that people are constantly exposed to phage regardless of whether they

receive live virus vaccines. Moreover, no obvious harm has come from injections with phage-bearing vaccines or phage alone.

Before antibiotics became widely available, people were "therapeutically" injected with phage when they contracted bacterial infections. The theory was that since phages specifically destroy bacteria, they could be used to treat these diseases. Representatives of pharmaceutical and serum firms say that even these deliberate injections with phage caused no apparent harm to people.

Lack of evidence of harm by phage, investigators at these commercial firms believe, should be weighed against the proposal that only sterilely collected serums should be used in the manufacture of live virus vaccines. They stress that increased costs, and possibly decreased availability, of vaccines in the future may not be justified by the hypothetical benefits of the elimination of phage. However, the serum processors are preparing for the forthcoming regulations requiring sterile serum, and they realize, as one representative said, that "the Bureau of Biologics had no choice in the matter." Once the phage contamination became known, public demand would have forced them to eliminate phage from vaccines.

Petricciani thinks that the Bureau of Biologics assessed all available evidence and came to a reasonable conclusion. Moreover, he disagrees with predictions of economic problems associated with the proposed regulations to rid vaccines of phage. The cost of serum, he says, is a very small fraction of the cost of a vaccine. And he agrees with the molecular biologists who claim that, as more and more details about the effects of phage on mammalian cells become known, serum distributors will likely discover that biologists whose research involves tissue cultures as well as pharmaceutical firms will demand sterile serum.—GINA BARI KOLATA

Quiet AAAS Meeting Dominated by Science Policy Talk

At the AAAS meeting in New York this year, quiet prevailed and attendance was down. By the last full day of the meeting, on 31 January, only 4250 paid registrants had been recorded, compared with 4700 at last year's meeting in San Francisco and the 6000 to 8000 expected. Meeting director Arthur Herschman and other AAAS officials attributed the low attendance mainly to the general economic situation. Moving the meeting out of the post-Christmas week may also have had an effect.

One consolation, though, was that the AAAS was not alone. A simultaneous meeting organized by the American Physical Society in Anaheim, California, drew only 1500—reportedly a thousand fewer than expected.

One impression widely shared at the AAAS meeting was that public policy sessions, which, in keeping with a recent trend, made up roughly half the program, were often under-attended while the more focused, hard-science sessions were frequently jammed. Possibly the best-attended session was a public lecture by the well-known writer Isaac Asimov, whose discussion of "the science fiction writer as prophet" drew a 3000 overflow crowd.

All of this led the AAAS board of directors and governing Council members to raise the possibility of increasing the research content of next year's meeting in Boston.

In its meeting this year, the Council focused on minority groups and problems of science and foreign policy. The Council approved a resolution recognizing the contributions to science by women and American Indians and urged the AAAS, as a policy, not to discriminate against scientists who are homosexuals, transsexuals, transvestites, or members of other "sexual minorities."

Other council resolutions deplored the recent barring of Israel from some activities of Unesco and urged other nations to favor maximum freedom for oceanic research at the upcoming United Nations Law of the Sea conference in Vienna.

Throughout, the radical groups once famous for disrupting AAAS meetings were quiescent, even though the issue of American involvement in Vietnam, formerly the source of radical anger, is reviving. A small representation from radical groups operated a literature table peaceably, though at prices that reflected the current inflation.

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Hallway talk at the AAAS meeting was that some of the scientific elite who have called on Vice-President Rockefeller recently have come away with the impression that a recommendation for strengthening the White House science advisory apparatus may be forthcoming within a month or two. Rockefeller is largely preoccupied with the probe of the Central Intelligence Agency he is heading for the President, but he nevertheless has staff working on the science advisory question.

According to one of the Vice-President's recent visitors, the White House decided in late December to elevate National Science Foundation (NSF) director H. Guyford Stever to a science counselor's post within the Executive Office, but then backed away from this decision under a hail of objections from the Domestic Council and the National Security Council (NSC). The lesson, according to this story, is that any new advisory arrangements will have to accommodate the independent systems of advisory panels that the Domestic Council and the NSC have built up in the 2 years since former President Nixon abolished the old Office of Science and Technology.

Stever, who has since had the title of President's science adviser, has established close relations with the Office of Management and Budget but the White House's two other main policy units have preferred largely to go it alone. The NSF's Science and Technology Policy Office has assumed a neutral stance in the debate over advisory structures.

Stever says that in fact no firm decision had been made or rejected to move him to the White House while leaving most of the advisory staff back in the NSF. He told *Science* that this is one of a number of options under consideration, and it is, he acknowledged, "some people's favorite model."—R.G. and D.S.