Assuming that such search techniques can be perfected, the ultimate goal will be to weave together many different kinds of libraries containing both text and nontext items into giant, multimedia libraries. Although the search software for different kinds of items may vary, says Terry Winograd, principal investigator for a consortium based at Stanford University, the user shouldn't have to worry about that. A student should be able to put in a single request for, say, information on the assassination of John F. Kennedy and receive a video of the shooting, a map of the final route JFK took through Dallas, text from newspapers, magazines, and books about the event, photos of Lee Harvey Oswald, and so on—all from dozens of sources around the Internet.

Besides the sheer power of having access to so much information, digital libraries offer another, potentially greater capability, says Bruce Schatz of the National Center for Supercomputing Applications and the University of Illinois, who is principal investigator for the Illinois project. In the past, libraries have provided for only a one-way flow of information—from the authors and other creators of information to the users. At most, a reader might write in the margins of a library book and thus offer something to future readers, but otherwise the information was fixed. Digital libraries offer a way for the users to play an active role.

The simplest way will be to offer annotating capabilities. Like the scribbler in a library book, users will be able to write notes to themselves and offer comments and extra information to any later user who wants to see what predecessors have added. Both the Illinois and Berkeley teams plan to offer this capability in their libraries. And Schatz and his colleagues are planning to equip their test library—a collection of thousands of articles on science and engineering—with an even more powerful interactive tool derived from Mosaic. A user who discovers an interesting relation between items will be able to set up links between them so that later users who called up one article would be referred to the others.

Ultimately, Schatz says, users should be able to add to the library themselves. A scientist might, for instance, take an equation from a journal article, use it to analyze data from another place on the Internet, use a visualization program from a third source to view the results, and then leave a record of the work for others to see and work with.

With this new suite of capabilities, the Internet would become something else altogether—a space of connected information instead of a collection of machines. Schatz calls it the "Interspace." Others may offer other names, but certainly no one will call it a used book store.

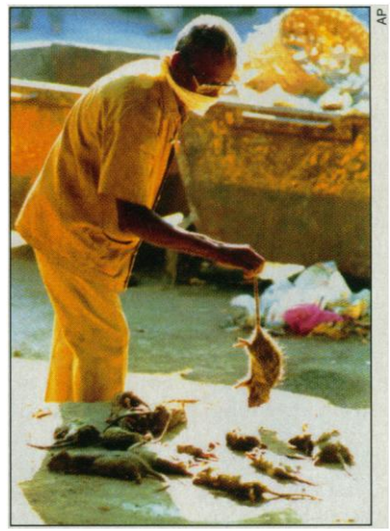
–Robert Pool

PLAGUE EPIDEMIC

Bottleneck Keeps Existing Vaccine Off the Market

As epidemics of deadly bubonic and pneumonic plague sweep India, no plague vaccine exists that can stop the epidemic in its tracks. There is a vaccine, formulated half a century ago, but it is far from ideal for halting an epidemic: It takes weeks to evoke immunity, and it does not provide permanent protection. No new vaccines have been developed in recent years, because there's little commercial incentive for companies to invest in an improved vaccine for a disease that rarely strikes industrial countries in significant numbers. As a result, promising leads on new vaccines haven't been followed up.

Even the current, flawed vaccine would be better than nothing, however—especially to protect vulnerable groups such as health or relief workers. But right now, it isn't commercially available in India—or in the United States. In India, 3-year-old stocks of the vaccine are only now being distributed by a government institute (see box on p. 23). And stocks in the United States, stored in the refrigerators of a small company in North Carolina, are not for sale. The reason: The U.S. Food and Drug Administration has taken nearly a year to confer its approval on the serum, even though the vaccine is identical to one that had been produced by another U.S. company for decades—and despite U.S. Army trials that have shown the vaccine to be safe and effective.



Thereby hangs a tail. Sanitation worker in Bombay collects rats; a bounty has been put on rats in that city to avert the spread of plague.

"It's heartbreaking to say there's nothing we can do," says William White Jr., president of Greer Laboratories, the small family-owned manufacturer located in Lenoir, N.C., which bought the rights to produce the plague vaccine 2 years ago. "We have a major plague in India, vaccine in the warehouse, people calling for it, and we can't get it to them." Most of those calling his company, White says, are relief groups and U.S. companies whose personnel work in the area.

The bottleneck holding up the plague vaccine in the United States results from FDA regulations. Those regulations require that if rights to a vaccine are sold to a new producer, the new company's preparation must be tested as if it were a new product—to ensure that the new company can consistently make a product identical to the one already approved.

Those regulations became a barrier to availability of the plague vaccine in March 1992, when Greer acquired the rights to the vaccine from Cutter Laboratories Inc. of Berkeley, California, a subsidiary of Miles Inc., which is itself an offshoot of the multinational A. G. Bayer Co. of Germany. The vaccine would bring Greer less than $2 million in revenues, but that is a significant sum for a company whose revenues are $10 million a year.

With no likely competition, Greer would have a virtual monopoly on the vaccine and a lock on the vaccine's sole significant U.S. customer—the Army, which must protect its troops in the event they are sent to a region of the world where plague is endemic. Patrick Murphy, professor of medicine at the Johns Hopkins School of Medicine, says "the Armed Forces are the only people who have a use for the vaccine, because the disease is so rare there's no reason to immunize the general population."

The Army's needs are not merely theoretical: The Cutter vaccine was an essential part of medical protection for U.S. troops in Vietnam. According to Walter Brandt, a civilian research employee of the Army, U.S. troops, all of whom were immunized, suffered only one case of plague per 1 million person-years of exposure. In contrast, the South Vietnamese army, which was not vaccinated, suffered 333 cases of plague per 1 million person-years of exposure.

Because of the armed forces' need for a plague vaccine, the testing of the Greer vaccine has been a collaborative effort between Greer and the Army. To satisfy the FDA's requirement that the Greer vaccine be identical to its predecessor, White says, the company used the same 50-year-old strain of the

India Scrambles to Distribute Vaccine

NEW DELHI—When pneumonic plague broke out last month in the industrial city of Surat, Indian authorities did not have an anti-plague vaccine that could be distributed immediately to those at risk. That's not surprising, given that the last known outbreak in India occurred 28 years ago. The only vaccine available—some 40,000 doses of a 3-year-old vaccine made from killed bacteria—were sitting in the freezers of the government's Haffkine Institute in Bombay, but before distributing them, authorities needed to test for potency and toxicity. For immediate distribution, health officials decided buying quantities from Russia was "the quickest way out," says Kamal Krishna Datta, director of the National Institute of Communicable Diseases (NICD) in New Delhi.

But this desperate reaction to a public health emergency turned out to be practically useless. Only after the vaccine arrived—and the directions were translated into English—did Indian officials learn it was a live-attenuated vaccine, meaning it's made from a weakened version of the live plague bacterium, *Yersinia pestis*, and produces mild—but still very uncomfortable—symptoms of plague. Because it packs such a wallop, says Datta, "it would not have been for general public use."

What's more, he says, those given the vaccine could not receive tetracycline, an effective treatment, because the antibiotic would kill the weakened plague bacteria and undo the vaccine's effects. Consequently, more than a week after they arrived, the 2200 doses of the Russian vaccine are still sitting in NICD freezers, from which they may later be removed—but only for scientific use by researchers.

But that setback did not leave public health officials defenseless. After 3 weeks of testing, the Haffkine Institute emptied its freezers of a vaccine developed in 1899 by its founder, W. M. Haffkine, a Russian scientist invited in by the British after a deadly epidemic swept through India in the mid-1890s. The vaccine provides 6 months' immunity in two shots, delivered about a week apart. A booster shot extends the protection to a full year, and the only side effect is slight discomfort from the shot itself.

Chand Goyal, managing director of the company, says he expects to have 150,000 doses available by the end of October, and that the institute is capable of producing as many as 1.5 million doses a month. The Indian authorities say they plan to distribute the vaccine to those in Bombay and elsewhere who are most likely to be exposed to plague victims.

–Pallava Bagla

Pallava Bagla is a science writer based in New Delhi.

plague bacterium (*Yersinia pestis*) that Cutter had used. To make the vaccine, this strain is killed with formalin; the dead cells are mixed with saline and preservative.

To make the process even more like Cutter's, Greer bought some of Cutter's equipment, which was trucked from Berkeley to Lenoir. The Greer vaccine is even stored in the same 4-foot stainless steel drums that held FDA-approved lots of the vaccine 2 years ago. Not surprisingly, given the fact that the production process is identical to the old one, the new vaccine performs the same as its predecessor. Brandt supervised controlled trials of the Greer vaccine involving 80 military personnel at Fort Sam Houston, headquarters of the U.S. Army Medical Command, in San Antonio. "We were satisfied that there was no difference between this vaccine and the old vaccine," Brandt said.

The results of the clinical trials were submitted to the FDA in October 1993. This July, as Greer waited for FDA approval, the U.S. Army's stockpile of plague vaccine ran dry, says Brandt. And there the matter rested until late September, when plague suddenly swept across thousands of miles of India after an absence of almost three decades. So far, the epidemic has caused at least 50 deaths and landed nearly 3000 people in isolation.

As the epidemic rages, Greer's refrigerators hold enough vaccine stock to immunize 280,000 people. White says his sales force has received more than 400 calls from prospective buyers—including the World Health Organization, UNICEF, and Citibank—since the first cases of plague emerged in Surat. (One call strikes him as particularly ironic. The caller was A. G. Bayer, parent of the company that used to make plague vaccine. Bayer wanted vaccine to inoculate its employees in India. White had to tell Bayer he could not legally provide it.)

This crisis could light a fire under the FDA. "I have notified the FDA of the extreme demand; they have notified us that they are reviewing the documentation as quickly as possible," White says. Arthur Whitmore, an FDA spokesperson, responded that the vaccine "is under review, but we're constrained from telling you when we would act on it."

But even if the Greer vaccine is approved soon, Murphy and some other experts are critical of the FDA's practice of making the new manufacturer of a time-tested vaccine "go through all that rigamarole from scratch." Murphy is especially critical in the case of plague vaccine, which, he points out, was "designed 50 years ago and hasn't changed." "It's ridiculous," Murphy says, "but the FDA dances to its own tune." Whitmore, however, said the practice of re-reviewing products is necessary to protect the public against imitations made with less care and expertise than the originals.

But even if the deadlock over the stocks of the Greer vaccine were resolved tomorrow, it wouldn't solve all problems concerning plague vaccines. Another concern is that there is little impetus for developing a better preparation, even though leads toward a better plague vaccine have existed for 3 years.

Thomas Schwan, a medical entomologist at the U.S. Public Health Service Rocky Mountain Laboratory in Hamilton, Montana, says his lab took the first steps toward a new vaccine 3 years ago. At that time, a postdoc in the lab, Warren Simpson, cloned the gene that enables the plague bacillis to produce a coating to protect it from host defenses when it is passed from a flea to a human. Simpson inserted the gene into *Escherichia coli*, which began churning out capsule protein. "It offered a high degree of protection to animals challenged with various doses of plague bacteria," Schwan says.

After a member of Schwan's lab presented the results at a conference, Army researchers requested the material to conduct their own experiments. Col. Arthur Friedlander, chief of bacteriology at the U.S. Army Medical Research Institute of Infectious Diseases in Frederick, Maryland, said his lab has inserted the coating gene into a new strain of *E. coli*, which is churning out a higher quantity of antigen. Preliminary studies have demonstrated that it does protect against plague infection. But because the market is so small, no company has shown interest in the new vaccine. As a result, there isn't a new and better plague vaccine on the market. And, as *Science* went to press, although sources close to the situation said Greer's vaccine could receive approval soon, for the moment stocks of the company's product are still sitting in the warehouse, off-limits to the world.

–Steve Sternberg

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