Vaccines Get a New Twist

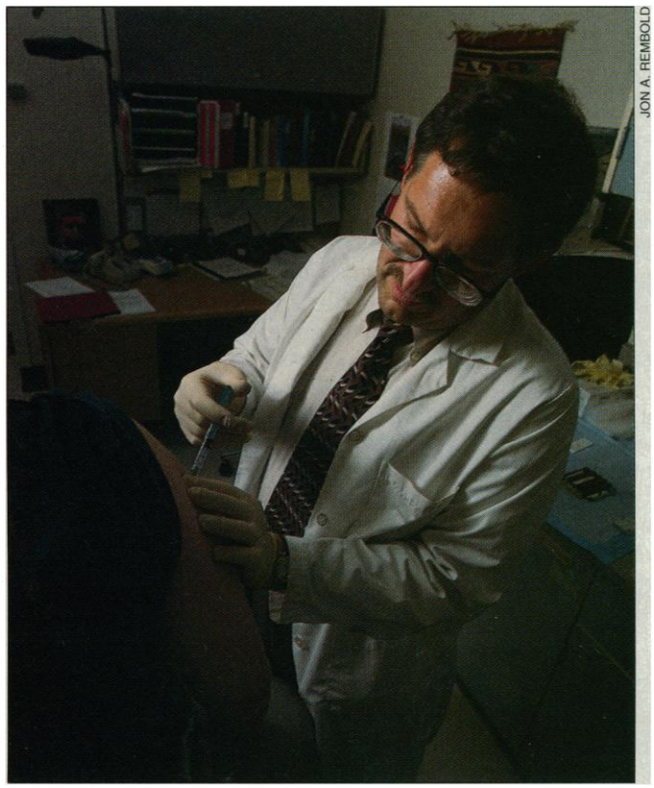
The new twist is that, in a dozen trials around the world, they're being used to treat disease—not just to prevent it—thereby shaking up some long-held medical dogma

Vaccines have probably prevented more disease than any other modern medical intervention except sanitation. That's a formidable record. Yet some researchers are making the somewhat offbeat claim that vaccines could have even more power: They believe vaccines can not only prevent illness, they can treat it. Lately the idea has received much publicity from efforts to boost the immune systems of people infected with HIV, but those efforts have yet to prove themselves and many researchers remain skeptical of the whole notion of therapeutic vaccines. Yet the AIDS studies are far from the only current examples of vaccines as therapeutic agents. In fact, a bumper crop of vaccine therapy studies for infectious diseases other than AIDS are now underway, but they have received precious little attention outside specialty journals and small scientific conferences.

Early data from those trials suggest that vaccines may well work as treatments. Indeed, researchers testing vaccines in people suffering from herpes, leprosy, tuberculosis, leishmaniasis, and hepatitis B have recently reported compelling evidence that it is possible to boost the immune response in infected people. "I think it's a much more important area than people recognize," says Harvard University's Bernard Fields, author of the classic textbook *Virology*. Moncef Slaoui, head of immunology/biology R&D at SmithKline Beecham Biologicals in Belgium, adds that "the field of therapeutic vaccines is blooming."

The main scientific reason many researchers have so far had little faith in vaccine therapy is that they don't believe it is possible to improve on the natural immune response. Once people are infected, conventional wisdom says, the immune system kicks in at maximum power, and if it can't do the job, the only rational course is to use drugs that attack the invader directly. Yet for more than a century, a few medical scientists have been challenging dogma, arguing that the immune system can be supercharged by a vaccine—even after infection. For some, "it's been an intellectually appealing strategy since the beginning of microbiology," says Colonel Donald Burke of the Walter Reed Army Institute of Research, who recently published a historical review of the subject in *Vaccines*.

There are several reasons why this strategy has practical, as well as intellectual, appeal. For many diseases, there are no drugs that work. In addition, vaccines might synergize with drugs, speeding recovery. What is more, a few shots of a vaccine over several months could be far more convenient than pills taken daily. And vaccines have the added advantage of causing few, if any, side effects. Those features were enough to fuel enthusiasm among proponents of therapeutic vaccines, but until recently, as Stephen Straus of the National Institute of Allergy and Infectious Disease (NIAID) puts it, "the level of enthusiasm aroused by this approach has always exceeded the facts."



JON A. REMBOLD

Getting better all the time. Lawrence Corey administers an experimental therapeutic vaccine for herpes infection.

Now, however, facts are beginning to catch up with enthusiasm. From New York to New Delhi, in the labs of biotech companies and university researchers, vaccine therapy is on a roll as researchers accumulate evidence that vaccines can boost immune responses in people infected with a variety of pathogens. And though investigators have yet to take the next step and show convincing health benefits from this supercharging, carefully designed tests are underway that will show whether this is possible.

Recurrent events

Advocates of vaccine therapy have few concrete examples to bolster their case. There is only one vaccine that has a solid track record of working in people who are infected—the vaccine for rabies, which Louis Pasteur first tested in human beings in 1885. Researchers believe this highly effective preparation triggers an immune response that hijacks the rabies virus on its journey up neural pathways to the central nervous system, where the virus runs riot.

That vaccine, however, has little in common with the modern push toward therapeutic immunizations. The rabies vaccine is a "post-exposure prophylactic," meaning that it is in essence a traditional vaccine—one that prevents disease—even though it's given after initial exposure to the virus. In contrast, the diseases at the center of the current renaissance of vaccine therapy all involve chronic, persistent infections that have already taken firm hold. The new therapies are aimed not at preventing disease but at keeping disease in check or curing it.

Of all the candidate therapeutic vaccines now being investigated, the preparation for herpes is the furthest along. Herpes simplex virus–type 2 (HSV-2) infects 20% of adults in the United States. Most frequently the virus is transmitted by genital contact, and it causes genital lesions that recur sporadically. In the mid-1980s, Lawrence Stanberry of the University of Cincinnati's Children's Hospital Research Foundation began using a guinea pig model to explore whether a vaccine could reduce the recurrence and severity of this latent infection.

His work was fruitful. In January 1988, Stanberry and Rae Lyn Burke, a virologist at Chiron Corporation in Emeryville, Califor-

nia, published a study in the *Journal of Infectious Diseases* showing that vaccines made from various concoctions of HSV-2 and HSV-1 (the related virus that causes cold sores) could reduce recurrence and severity of herpes lesions in guinea pigs by about 50%. "We were very excited about those results," recalls Stanberry. But his enthusiasm was tempered by the fact that "a number of people basically didn't believe [the results]."

Burke and Stanberry are now working on separate trials of HSV vaccine therapy in humans. In 1989, Burke and scientists at Ciba-Geigy—who work with Chiron in a joint venture called Biocine—began tests of a preparation made from a cloned surface protein of HSV-2, gD2, mixed with alum, an "adjuvant," or immune-boosting addition to the preparation. After no serious toxicity was seen in safety studies, NIAID's Straus and Lawrence Corey at the University of Washington launched a placebo-controlled study in late 1990 with 98 patients.

Last May, the researchers presented encouraging initial results: Vaccinated patients had 30% fewer recurrences. Those results were a rejoinder to prevailing wisdom, Corey says, because they demonstrated that "you can give an immunogen to someone already infected and have a positive clinical outcome." Stanford University's Thomas Merigan, who once collaborated with Burke and now studies HIV, was also impressed with the capacity of these results to break new ground. "There was no precedent for it," says Merigan, who heads Stanford's Center for AIDS Research. "It is really a new idea that needs to be explored."

Corey and Straus both caution that these cheering data must be kept in perspective. They note, for instance, that there is no desperate need for a herpes therapeutic vaccine because acyclovir, a drug already licensed to treat herpes infection, reduces recurrences by 90% or more. Still, Straus and Corey say if a vaccine were as effective as acyclovir, it would be an attractive option. "Acyclovir, to be effective, has to be taken twice a day every single day for years," explains Straus. "For some people, if they could get a shot once or twice a year, that's preferable."

Stanberry, in the meantime, has hooked up with Slaoui at SmithKline Beecham, which has its own therapeutic herpes vaccine trials underway. This month they began a 100-person, placebo-controlled trial of the gD2 surface protein mixed with alum and a second adjuvant, MPL. Slaoui says much is riding on the results of this trial, which should be finished by the end of 1995. "This is a concept we'd like to further seriously consider for many chronic diseases," says Slaoui. "The success of these early trials will be critical for how much we go forward in that direction."

Zero tolerance

As in the case of herpes, good drugs exist to combat leprosy, which is a chronic infection with *Mycobacterium leprae* that can lead to severe nerve damage and deformity. But, as in the case of herpes, an effective therapeutic vaccine might have something to offer. In the first place, the multidrug treatment for leprosy often takes several years to clear the bacillus from an infected person's system. Second, drug treatment does not correct underlying immunologic defects that may predate infection; in some people, cell-mediated immunity (CMI), the arm of the immune system that kills cells infected with *M. leprae*, doesn't kick into action. Finally, some patients are simply resistant to drug treatment.

Faced with these drawbacks in conventional treatment, Jacinto Convit, director of the Institute of Biomedicine in Caracas, Venezuela, in the 1970s began exploring whether vaccine therapy could help his leprosy patients. He concocted a cocktail vaccine consisting of killed *M. leprae* and the vaccine for preventing tuberculosis, BCG, a preparation also made from a mycobacterium.

As Convit reported at a 1986 symposium on the Immunology of Leprosy held in Norway (and published that year in *Leprosy Review*), in uncontrolled studies, a combination of the vaccine and drugs seemed to restore the cell-mediated response to *M. leprae* in 60% of more than 300 patients with severe forms of the disease. The CMI, in turn, cleared *M. leprae* from their lesions and left some patients less vulnerable to relapse or reinfection. In effect, their immune systems had been boosted to the point where they no longer tolerated the bacillus.

The specific benefits of the vaccine, says Convit, showed up clearly in these trials: The vaccinated patients' lesions were under control within 2 years, half the response time for patients on drugs alone. In addition, Convit claims to have had success treating patients who did not respond to drugs. "I've seen some of those patients, and there's little question that they were cured," says Barry Bloom, a Howard Hughes Medical Institute researcher at the Albert Einstein College of Medicine, of the previously untreatable cases. G. P. Talwar of the National Institute of Immunology in New Delhi, India, has tested a different therapeutic leprosy vaccine and reported similarly encouraging findings.

But these apparent successes haven't by any means quashed skepticism about the potential role of therapeutic vaccines in treating leprosy. Convit's colleagues would like more evidence that his concoction works. "The results are better than anyone anticipated, but more experience is required in other settings in other countries," says Gerald Stoner, a researcher at the National Institute of Neurological Diseases and Stroke who spent 5 years in Ethiopia working with leprosy patients. William F. Ross of the American Leprosy Missions International has even stronger reservations. "I'm really rather skeptical about it," says Ross, who believes Convit's trials needed to have more standardized protocols for vaccination schedules and doses and for evaluating responses. "It's all a bit higgeldy-piggeldy, so it makes interpretation difficult."

The skepticism about trials of therapeutic leprosy vaccines pales next to the doubt that greets trials of vaccines aimed at treating tuberculosis. Attempts to fashion a therapeutic TB vaccine date all the way back to Robert Koch, the German microbiologist who in 1882 isolated *Mycobacterium tuberculosis*, the pathogenic bacillus.

Koch tried to fashion a vaccine from the killed organism, but his dream that this would lead to a cure for tuberculosis failed miserably when his preparation likely caused angina, delirium, and coma. The dream has never died, however, even though powerful anti-TB drugs now exist. Its latest proponent is John Stanford of the University College London Medical School. Stanford initially was puzzled by the finding that the preventive TB vaccine, BCG, performs well in some countries but not in others. He thought perhaps there was something in the environment in the countries where it worked, such as Uganda, that had affected the vaccine's perfor-

On a Roll: Vaccine Therapies

Companies/Investigators	Disease	Stage of Trials
Biocine, Rae Lyn Burke	Herpes	Phase II*/III*
SmithKline Beecham, Moncef Slaoui	Herpes	Phase II
Jacinto Convit	Leprosy	Phase III
G. P. Talwar	Leprosy	Phase II/III
Jacinto Convit	Leishmaniasis	Phase III
John Stanford	Tuberculosis	Phase III
Christian Brechot	Hepatitis B	Phase II
Vical	Hepatitis B	Animal studies
Cytel	Hepatitis B	Preclinical
Viagene	Hepatitis B	Preclinical

*Phase II-typically small trials for safety and immunogenicity; Phase III-large efficacy trials.

mance. This hunch led Stanford to *Mycobacterium vaccae*, a cousin of *M. tuberculosis* found in Ugandan soil.

Working with Graham Rook, also of the University College, and J. M. Grange of London's National Heart Hospital, Stanford began testing a vaccine containing killed *M. vaccae* in patients who had TB. As reported in a paper in press at *Clinical Immunotherapeutics*, they have tested this vaccine in several countries and claim to have cut the failure rates of drug treatment in half and reduced deaths during treatment. In data pooled from trials in Gambia and Vietnam, they report that 89% of the patients treated with anti-TB drugs and vaccine were cured, compared with 78% of patients receiving drugs and a placebo injection; deaths dropped from 8% to 3%. "I think this treatment is going to be very important," says Stanford.

"The field of therapeutic vaccines is blooming."
—Moncef Slaoui

One reason for his optimism is that the *M. vaccae* vaccine may cut the time required for conventional drug treatments to work. TB takes about 6 months to treat with drugs, and many patients don't complete the therapy, letting the disease linger—and giving the bacillus a chance to become resistant to drugs. "If we could get it down to 2 months, treatment of TB would change overnight," he says, "and I think it could be done." He also has reported evidence in *Lancet* that his vaccine works in people with multi-drug resistant strains of TB.

But Stanford and his co-workers have a long way to go before they convince their colleagues. Epidemiologist Paul Fine at the London School of Hygiene and Tropical Medicine has been among the critics. "I'm skeptical about the evidence produced so far," says Fine, who says the trials to date have not been well controlled. Yet Fine keeps an open mind—open enough, in fact, that he has been appointed official monitor of a trial of the vaccine in 400 TB patients in Durban, South Africa. "I desperately hope this stuff works," says Fine, "but I'm going to be a skeptic until it's proven."

If the leprosy and tuberculosis vaccine therapy data are too squishy for some, Convit has more solid data that the approach has merit in leishmaniasis, a disease caused by a protozoan that leads to lesions, tissue destruction, and deformity. As in the case of herpes, leprosy, and TB, there is a drug treatment for leishmaniasis, meglumine antimonate, and it is highly effective. But the drug carries the risk of serious side effects, including cardiovascular complications. So Convit developed an immunotherapeutic vaccine containing a mix of BCG and killed leishmania to see if it could cure the disease without drugs.

This vaccine, which Convit tested in Venezuela in collaboration with Bloom, has had remarkable success, probably because it boosts the cell-mediated immune response. In a blinded 94-patient trial comparing vaccine and drug, both treatments had a 95% cure rate, Convit and Bloom reported in *Lancet* in 1987. More to the point, only 6% of the vaccinated group reported side effects—compared with 52% of those who received the drug. Though the vaccine works a little slower than the drug, Convit points out that it costs only about $30 for the complete series of injections; the full drug regimen costs almost $300.

While drugs can effectively treat herpes, leprosy, leishmaniasis, and TB, there is no effective treatment for infection with hepatitis B virus (HBV), which afflicts 300 million people around the world, causing cirrhosis and even liver cancer. This makes HBV a prime target for vaccine therapy. Adding to the belief that this strategy can work, studies done more than a decade ago to test a preventive hepatitis B vaccine—which is now on the market—gave strong hints that it might have some potential as a therapeutic, too.

On the horizon

The only test of the approach in HBV-infected humans so far was reported last year by Christian Brechot of France's Necker University and the Pasteur Institute's Marie-Louis Michel and Stanislas Pol. In *Compte Rendus de L'Academie des Science*, the French researchers said they treated 14 patients who were chronically infected with HBV using a vaccine made from a surface protein of the virus. After 6 months, the researchers claim, HBV could not be detected in three patients. Another four had detectable, but significantly decreased, amounts of HBV. In comparison, in a historical "control group" of 34 patients who were followed for 40 months, only three spontaneously rid their bodies of HBV. "This was very striking for us," says Brechot.

Once again, the skeptics are raising red flags. Jay Hoofnagle, a hepatitis researcher at the National Institute of Diabetes and Digestive and Kidney Diseases, is doubtful the approach will pan out. "I can't see how it could make a difference because people with hepatitis B have a lot of antigen [viral fragments] in their blood—a lot more than you can give them in a vaccine." Therefore, Hoofnagle reasons, their immune systems should already be at the maximum level of response. "It doesn't make sense." Brechot counters that the vaccine presents the HBV antigens to the immune system by a different route from the one they normally take, an idea Hoofnagle allows is "reasonable" but not overwhelmingly convincing.

Several trials now underway could give insights into who's right here—the skeptics or the believers. A controlled trial of the French therapeutic vaccine is now gearing up, with plans to enroll more than 150 patients in six European countries. And three biotech companies—Vical, Viagene, and Cytel, all of San Diego—are conducting preclinical tests of candidate HBV vaccines.

With these trials and many others now underway, the vaccine therapy faithful feel it's only a matter of time before the approach proves its worth. "Ultimately, what's going to happen is people are going to recognize in retrospect that the immune system is fairly clever and that one can reduce it to a minimalist level and manipulate each component," predicts the University of Cincinnati's Stanberry. "At that point, everyone will say that vaccine therapy makes sense." Not everyone is saying that yet. But the chorus is far louder than it was just a couple of years ago. And it's likely to become even louder and more tuneful as the results continue to roll in from vaccine therapy trials around the world.

–Jon Cohen

Additional Readings

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