New Hope for Vaccine Against Schistosomiasis

A parasitic disease that afflicts 200 million people is proving a wily foe, but some candidate vaccines are showing promise

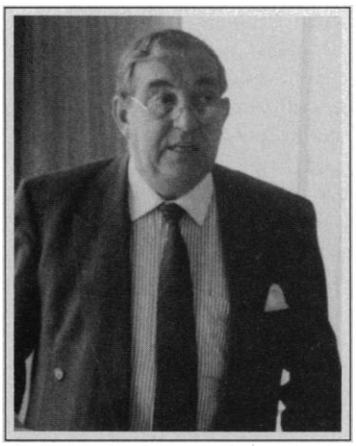
Geneva—IN THE TIME-HONORED TRADITION of vaccine developers, immunologist André Capron is about to become a human guinea pig. In the next few weeks, he plans to inject himself and a dozen or so volunteers at his lab in northern France with his new genetically engineered vaccine against the parasite that causes schistosomiasis. If Capron's vaccine ultimately proves effective—the test on himself will determine only if it is safe—it could provide a powerful new weapon in the fight against this debilitating disease that afflicts some 200 million people in the Third World and threatens a further 500 million to 600 million.

The prospect has World Health Organization officials excited, and that's somewhat ironic. The WHO long argued that a schistosomiasis vaccine wasn't needed because the disease can be controlled by drugs and sanitation alone. Praziquantel, the drug of choice, will kill the adult worms, but people become reinfected from larvae that multiply in water snails. Either you give praziquantel once a year, or you clean up the water. Preferably you do both. But WHO's optimism wasn't enough to achieve control. Indeed, WHO itself acknowledges that since 1984 schistosomiasis has spread to 2 more countries—76 in all.

So Capron's work—and advances by a handful of other researchers around the world who are also closing in on potential vaccines—has convinced WHO officials to broaden their armamentarium against the disease. The organization's change of attitude was evident last week when WHO officials gathered a group of experts on schistosomiasis at a meeting here to outline strategies for the further development of a vaccine. Proclaimed Tore Godal, director of WHO's program of Tropical Disease Research, "Schistosomiasis vaccine development has a very high priority. It is a big hole in our repertory."

One reason WHO had been skeptical of schistosomiasis vaccines was that the parasite seemed too wily a foe to succumb to a vaccine. The disease is caused by a small worm that has evolved many methods for evading the host's immune system, from secreting substances that mimic the host's antigens to absorbing the host's own antigens as a disguise. Once they have slipped past the body's defenses, the parasites take up residence in blood vessels. Adult worms lay thousands of eggs, some of which lodge in small veins, especially in the liver, where they pump out antigens that trigger an immune response in the host. This results in the formation of a large, fibrous mass of scar tissue that eventually blocks the blood flow, starving the liver of blood and causing the enlarged and hardened liver that is one hallmark of schistosomiasis.

Vaccine researchers refused to be discouraged by these arguments, instead taking heart from the fact that, although the adult worm can make itself invisible to the host's immune system, there is evidence that people do acquire immunity to schistosomes. After treatment with praziquantel, adults are less likely to become reinfected than children, even though they may spend as much time in infected water. After years of infection adults presumably build up some sort of immunity—probably by attacking the more vulnerable larval stages—and a few parasitologists have sought to mimic it with a vaccine.



Guinea pig. *Immunologist André Capron is about to test a vaccine on himself and other volunteers.*

Though finding a chink in the parasite's immunological armor has been tough, researchers have one key advantage: A schistosomiasis vaccine need not be perfect. "You don't need 90, or 99, or 99.9% protection, as you do with viruses or bacterial disease," says Anthony Butterworth, a parasitologist at the Department of Pathology of Cambridge University, who has been studying schistosomiasis in Kenya for more than 20 years. Debilitating symptoms of the disease generally appear only in people who harbor large numbers of parasites, so if a vaccine is effective in reducing everyone's burden of worms by, say, 50% or more, it can dramatically reduce the number of severe cases of the disease.

Capron, director of the Center for Immune Biology of the Pasteur Institute in Lille, says he has been searching for such a vaccine for 32 years. His group has cloned more than ten genes that code for various proteins produced by the worm. The most promising is one he calls p28GST, which is derived from a protein secreted by the excretory system of the adult worm. It seems to be a member of the family of enzymes called glutathione *S*-transferases, but as yet its function in the worm is not known. However, a single injection of p28GST offers what Capron calls "a significant degree of protection" from schistosome infection, up to 59% fewer worms in the rat and around 40% in the baboon. More important, immunized animals excrete some 65% fewer eggs per day. In fact, there are two effects at work, one that makes the female worm less fecund—she lays fewer eggs each day—and another that makes those eggs less viable. The two seem to depend on distinct domains of the p28GST molecule; reduced fecundity requires p28GST to work as an enzyme, while reduced viability does not.

A first experiment on cattle in Sudan, which are infected by a bovine variety of schistosome, succumbed to the 1988 drought. Vaccinated cattle were immunized and released, with the intention of checking them regularly for natural infections. But, says Capron, "there was no rain, no snails, and no infection." Last year a second, less ambitious experiment, which involved deliberately challenging immunized calves, revealed the potential of p28GST to protect cows against schistosomiasis. Vaccination reduced the adult worm burden by 54%, the number of eggs in the feces by 83%, and the number of eggs in the tissues of the intestines by 97%. Since it is the eggs that cause the symptoms, this is a very encouraging result.

Though Capron's candidate vaccine is closest to human trials, several other groups are reporting promising results from alternative strategies. Jim Young, vice president for research and development at MedImmune, Inc. in Maryland, is genetically engineering BCG (bacillus Calmette-Guerin), currently used against tuberculosis, into a vehicle for carrying schistosome (and other) antigens. He points out that BCG has an excellent safety record—having been given to some 2 billion people without untoward

effects—and is very good at stimulating the host's immune system. Moreover it is cheap, needs no complicated cold chain to keep it in good condition from factory to field, and can be given orally.

Young's company has inserted antigens for several diseases into genetically engineered BCG. Paramyosin, a worm protein coded by a gene called Sm97, has been put into BCG and injected into mice, who responded well to a challenge with paramyosin or whole worm extract 8 weeks later. While these are very preliminary results, Young says he is "hopeful that [engineered BCG] could be a different way of immunizing against schisto."

Don Harn, a biochemist at Harvard University's School of Public Health, has cloned yet another aspirant antigen, triose phosphate isomerase or TPI; unpublished results indicate that it protects mice from schistosome infection. And another glutathione *S*-transferase, isolated from *Schistosoma japonicum* by Graham Mitchell while at the Laboratory of Immunoparasitology of the Walter and Eliza Hall Institute of Medical Research in Melbourne, Australia, also looks promising. But the existence of at least four good antigens raises an interesting problem: Who will decide among them? "Why do you want to put all of your eggs in that one GST basket?" asked Jim Young. He suggested that WHO consider taking on the chore of standardized assessments in independent laboratories, an initiative the panel supported. Even Capron, who is ahead at the moment and might be thought to have the most to lose, agreed, though he insisted that any candidate be proven in many animal models before he would hand over p28GST for head-to-head laboratory trials.

A choice could prove difficult. Peter Reeve, of the product development unit in WHO's TDR, said, on the basis of what he knew about the candidate vaccines, that WHO "is impressed by p28." He also conceded "a compelling case for BCG." Godal pointed out the pitfalls: On the one hand an early commitment to one vaccine could stifle development of others that might be better, while on the other a lack of commitment could hinder testing of even the best candidates. "Late pre-clinical and early clinical trials are the hardest to finance," Godal noted. "We must find a way to cover them without undermining the other things in the pipeline."

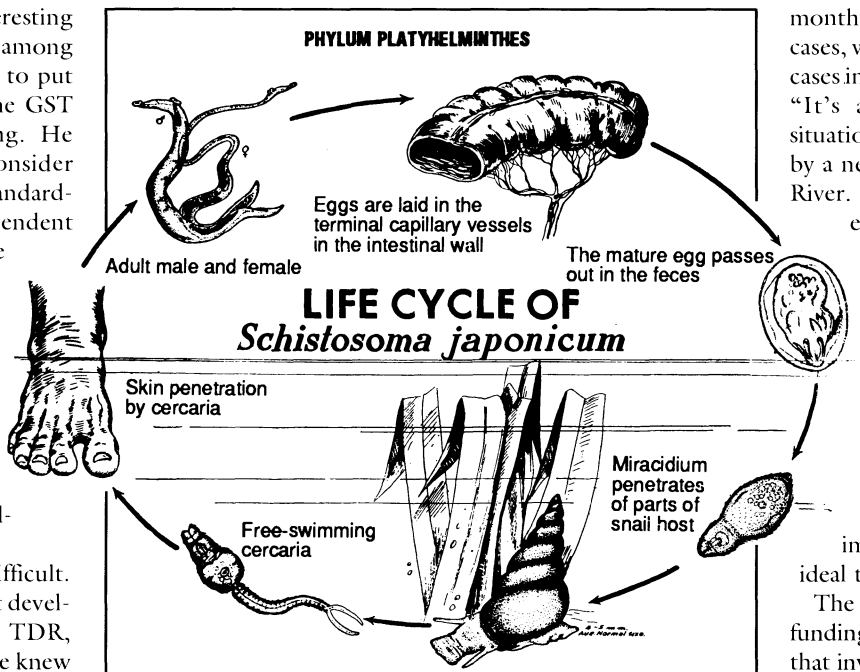
But despite the general optimism of the panel at WHO's meeting, the vaccine developers still have some convincing to do. "Won't an annual dose of praziquantel be as effective?" asked John Dunne, director of drug management and policies with responsibility for ethics at WHO. Capron shook his head and muttered "they can't afford it." Furthermore, praziquantel must be given at least once a year and, as Godal pointed out, is at present reaching only 5% to 10% of infected people compared to the 70% or 80% of the world's children being reached by WHO's extended vaccination program for childhood diseases.

One possible concern is that an effective vaccine could undermine the power of praziquantel. Evidence is accumulating that the drug seems to need the host's immune system to enable it to kill the worms. Vaccination might stimulate one specific part of the immune response, sufficient to deal with invading worms, but cause other parts to be lacking. What will happen when vaccination becomes prevalent if some as yet unknown part of the immune response to schistosomes is lacking? The drug could become ineffectual.

Another worry is that Capron's p28GST, because it belongs to a family of enzymes also found in humans, could cause autoimmune disease, causing the immune systems of vaccinated people to turn against their own tissues. But Capron insists that he has looked carefully for cross-reactivity between the antibodies to p28GST and normal human proteins: "None can be found with any technique." There is a weak reaction with a GST found exclusively in human placenta, and Capron says he is working to remove a couple of amino acids from one end of p28GST to eliminate even that weak cross-reactivity. He is also creating a "hedgehog" molecule, whose spikes bear several copies of regions of p28GST that seem particularly important in eliciting an immune response.

Assuming that Capron's self-inflicted safety tests reveal no hidden difficulties, the first trials of efficacy are likely to take place in Senegal, where there has been an epidemic outbreak of schistosomiasis around the town of Richard Toll. The first case of schistosomiasis there was identified on 13 February 1989. By the last 3 months of 1989 there were 2500 cases, which climbed to 6000 new cases in the first 3 months of 1990. "It's an absolutely incredible situation," says Capron, caused by a new dam across the Sénégal River. Previously salt water penetrated far inland, keeping the snails at bay. The dam prevents that, and along with the increase in snails came an increase in irrigated agriculture and an epidemic of schistosomiasis. Most of the adults have not been infected before, so they have not acquired natural immunity, thus providing an ideal testbed for the vaccine.

The European Commission is funding a schistosomiasis network that involves ten labs in Europe, a treatment center in Senegal, and a 5-year program of which the vaccine could be one component. The next 2 years will see "very serious scientific work" in which epidemiologists and immunologists will establish baseline data. Capron hopes that by the time they are done he will have permission to try his vaccine in earnest. "I don't see why we should wait any more," he said. ■ JEREMY CHERFAS



Death cycle. Schistosomiasis is caused by a small worm that takes up residence in blood vessels. Two varieties, *Schistosoma mansoni* and *S. japonicum* live in veins near the intestines. The third, *S. haematobium*, lives in blood vessels around the bladder. All three have similar life cycles. The disease is endemic in tropical areas with poor sanitation, which permits excreted eggs to enter lakes and rivers. Snails are an essential link in the chain, providing a host for the larval stage. (From Noble, E.R., *et al. Parasitology*, 6th ed., Philadelphia, Lea & Febiger, 1989, p. 176. [Modified from Pesigan, courtesy of Santo Thomas J. Med.])