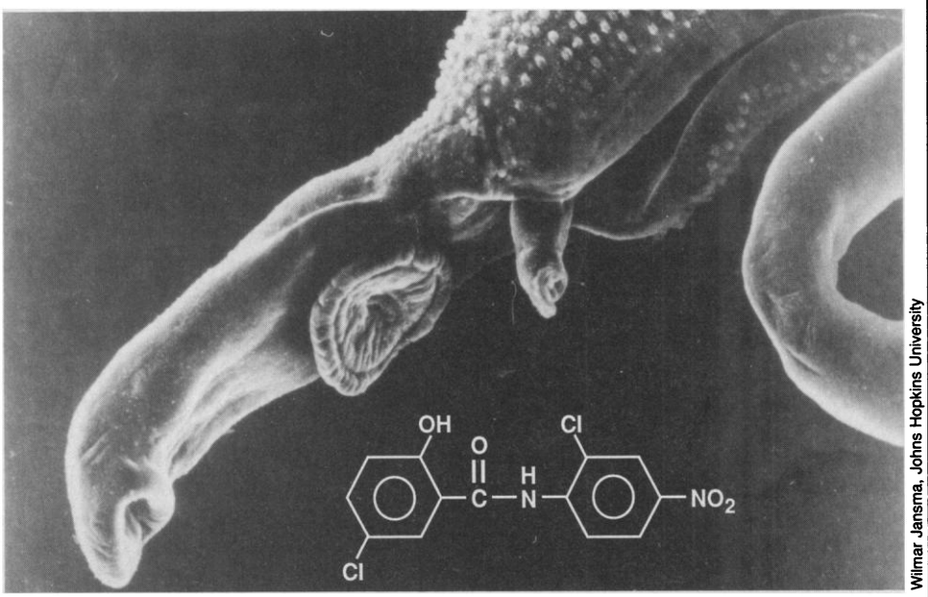
New Weapon in the War Against Schistosomiasis

Research by the U.S. Army has turned up a compound that prevents infection by the schistosomiasis parasite



Wilmar Jansma, Johns Hopkins University

Public enemy, public weapon. *A pair of mating* Schistosoma mansoni, *cause of the tropical disease schistosomiasis, alongside a formula for the U.S. Army's new defensive weapon, niclosamide.*

THE U.S. ARMY is about to start testing an antipenetrant with a difference. Instead of keeping armor-piercing projectiles out of tanks, the Army has a drug it expects will keep the schistosomiasis parasite out of the human body. That may keep troops healthy in infested areas of the world, but many experts believe it is unlikely that the Army's new medication will help those who need it most—the hundreds of millions of people in the Third World who are exposed to *Schistosoma*, public enemy number two on the World Health Organization's list of top ten scourges.

The compound, niclosamide, has a long track-record as a killer of the snails that harbor *Schistosoma* and, taken internally, as a drug that kills parasitic worms. Now, Army research has indicated that, when used in a lotion, it effectively blocks *Schistosoma* from entering a human host. The lotion prevents cercariae, the microscopic swimming stage of *Schistosoma*, from penetrating the skin. Since cercariae are the only stage in the parasite's life cycle capable of getting through the body's defenses, if you stop them, you prevent infection.

So far, the preparation works perfectly in mice and monkeys. Next stop, man. A niclosamide lotion is about to enter phase I trials at Johns Hopkins University Medical School to determine whether it causes any adverse reactions. Phase II trials, slated to start in Egypt and Brazil next year, will establish the lotion's efficacy at preventing infection.

Schistosoma is a blood fluke that generally lives in the veins of the gut and liver of its human host. Adult worms can survive up to 20 years, and heavy infestations block blood vessels. The mere presence of even a few adults acts as a focus of inflammation and infection. Worse, the females release thousands of eggs each day, which often find their way to tissues such as liver, brain, and lung, where they cause considerable damage by stimulating the body to form cysts and scar tissue around them.

Most eggs, however, pass through the bladder or wall of the gut. Once outside, they hatch and infect water snails. The parasite multiplies inside the snail, giving rise to thousands of cercariae that exit the snail and swim free in search of a mammal in which to complete their life cycle. When the cercaria makes contact with skin it releases enzymes that dissolve the protein of the skin, affording easy entry.

The WHO estimates that some 200 million people worldwide suffer one or another of the forms of schistosomiasis. Only malaria causes more sickness and debility. But that is not why parasitologists at the Walter Reed Army Institute of Research (WRAIR) are worried about it. They recall 1944, when *S. japonicum* was a serious threat to the push to retake Leyte in the Philippines. "Many units had in excess of 80% casualties," says Lieutenant Colonel Willis Reid, chief parasitologist at WRAIR. He's not talking about walking wounded; he's talking about seriously infected U.S. soldiers. Especially badly hit were members of engineering units, who spent much of their day in infested water. As Reid notes, "When you get a critical bridge-building unit knocked out of action, that can be detrimental to the mission."

Treatment, which today is safe, effective and available, comes too late for the Army, which wants to keep troops healthy, not heal them when they are already sick. The Army's answer was to screen a cupboard full of compounds to see if any could prevent infection. In 1982, Captain Robert E. Miller recognized that the most promising compounds were all so-called salicylanilides. Miller's search of the Army's database of chemicals revealed that niclosamide was also a salicylanilide, and in animal tests a single application proved able to block penetration by cercariae for 7 days or more.

Other salicylanilides were even more effective antipenetrants, but the army chose not to pursue them. "We went with niclosamide because it was already on the market, albeit for different uses," says Willis Reid, "so there was plenty of information on it available."

The long-lasting protection is thought to be the result of niclosamide binding chemically with the outer layers of the skin. Researchers speculate that the enzymes that the cercariae secrete to get through the skin sever the bond between niclosamide and skin, releasing the compound which then kills the cercariae. "Wearing off might actually be a matter of skin turnover," says Reid.

Field trials will probably take place among rice growers in the Nile delta and farmers in the Bahia region of Brazil who spend much of their time in infested waters. "The biggest problem we have is ethical," says Miller, who is now at the U.S. Army Medical Research Unit in Rio de Janeiro. "You can't ask anyone who has not been infected before to test the product," because the first infection can be very severe. The trials will measure re-infection among people who have been treated to eliminate the disease. They will be given either niclosamide or a

placebo to apply to the skin.

Army researchers are confident that niclosamide will come through the trials as a safe and effective lotion to prevent infection by cercariae. That will suit the military need to keep troops healthy. But will it help the 600 million people who live with the threat of schistosomiasis?

Gerald Webbe, professor of Applied Parasitology at the London School of Hygiene and Tropical Medicine, doubts it. "I am really skeptical about topical applications," Webbe told *Science*. "Good sanitation and improved quality of life are the real answers."

Webbe has 30 years experience of schistosomiasis in the lab and in the field, and it was he who discovered in 1975 that concentrations of niclosamide too low to kill snails nevertheless killed cercariae. He thinks that lotions and creams will not be made available because there is no market among the desperately poor people who are most exposed. And even if they were available, Webbe says local people would not use them.

One U.S. Army source agrees. He said that countries where schistosomiasis is endemic have not been clamoring for topical niclosamide. "A lot of Third World countries are not interested in protecting their people, they're interested in protecting their military. There's not much of a market."

Miller, who discovered the topical antipenetrant, is more sanguine. He thinks niclosamide could have a "tremendous impact" on endemic schistosomiasis, especially in combination with chemotherapy to treat the disease and programs to slay snails. Miller concedes that the lotion might be impractical because it has to be applied carefully and regularly. But his colleague Reynaldo Dietze, associate professor at the School of Medicine of the Federal University of Espirito Santo in Brazil, is working on a niclosamide soap that Miller thinks could be the answer. "These are very hygienic people," he says of the Brazilian farmers he has been working with. A soap containing 0.1% niclosamide would be effective and cheap. "It costs more to put the wrapper on the soap," says Miller.

If anyone ought to know what might become of the army's new product, it is the manufacturers. They would exploit it if they thought it worthwhile. Miles Laboratories, the U.S. arm of Bayer, the German company that originally developed niclosamide to kill snails, has been working with the Army on the antipenetrant. Charles Woodruff, director of product development at Miles, told *Science* that the company has no plans to make topical niclosamide more widely available. ■ **JEREMY CHERFAS**

Superconductivity: Party Time Again

Only 6 months ago, many superconductivity scientists were worried that their party was nearly over, cut short by the presence of an uninvited guest called "flux lattice motion"—a weakness in high-temperature superconductors that appears in the presence of high magnetic fields and large electrical currents (see *Science*, 26 May, p. 914). But in the past few weeks, researchers have reported several remarkable advances that imply that this particular problem can be fixed. As a result, the mood among scientists in the field is markedly more upbeat than only a short while ago.

The most recent advance was announced by Sungho Jin of AT&T Bell Labs at the 1989 Fall Meeting of the Materials Research Society in Boston, 27 November to 2 December. Jin and co-workers produced bulk samples of the superconductor $YBa_2Cu_3O_7$ that could carry nearly ten times as much current as the best bulk materials made by standard processing techniques. At 77 K and in a 0.9 tesla magnetic field, the samples had a critical current density of 100,000 amperes per square centimeter.

High-temperature superconductors are useful because they lose all electrical resistance when cooled by liquid nitrogen, which has a boiling point of 77 K. Their usefulness has been restricted, however, by a limitation in the maximum amount of current they can carry before losing their superconductivity. The problem is not a big one for superconducting thin films, which will be used in electronics applications, because they have shown relatively high critical current densities. But the densities in bulk samples have until recently been too low for use in such applications as motors and large-field magnets.

Early this year, researchers discovered that one reason for the problem was the weakness of the so-called magnetic flux lattice in the high-temperature superconductors. When these materials are placed in a strong magnetic field, the magnetic flux flowing through the superconductor splits into individual lines which arrange themselves into an ordered array—the magnetic flux lattice. When an electric current passes through the lattice, it exerts a force that pushes on the magnetic flux lines. If the lines are not somehow pinned in place, the electric current will force them to move, which dissipates energy and ruins the perfect superconducting state of the material. The flux lattice in low-temperature superconductors can be pinned rather easily, but scientists had worried that the lattice in the high-temperature materials might be so weak they could never carry much current in a magnetic field.

The one hopeful sign was that thin films of high-temperature superconductors could carry plenty of current, which meant that they somehow avoided the problem of flux lattice pinning, but no one knew exactly how they did it. The work by the Bell Labs group may explain what is going on in thin films, Jin says, and it should point the way to forming bulk samples with usefully high critical current densities.

The Bell Labs technique depends on a clever processing trick, Jin explains. It starts with a sample of $YBa_2Cu_4O_8$, which is a slightly modified version of the $YBa_2Cu_3O_7$. Heating the sample rapidly to 920°C causes it to change into $YBa_2Cu_3O_7$. The process leaves extra copper and oxygen atoms in the sample, much as a round of musical chairs leaves one player without any place to sit, and the presence of these extra atoms scattered throughout the material creates many tiny defects in the sample. The defects apparently act as pinning centers, helping to hold the flux lattice in place and increasing the critical current density by a factor of 10.

Less than a month ago, another Bell Labs team announced it had increased the critical current density in single crystals by exposing them to neutron radiation (see *Science*, 10 November, p. 755). The same process of creating tiny defects in the superconductor appears to be at work in both the rapid heating and neutron bombardment techniques. The neutron irradiation method probably would be difficult to commercialize, however, because it adds a costly step to the manufacturing process. Jin's technique depends only on a modification of the usual fabrication method and thus is more feasible for transfer to a large-scale process.

Jin suggests that the new results may help explain why thin films of superconductors seem to have inherently high critical current densities. Work by Theo Siegrist of Bell Labs shows that when a thin film of $YBa_2Cu_3O_7$ is produced, it must first go through a $YBa_2Cu_4O_8$ phase. Thus, Jin suggests, his group's technique may be merely reproducing in bulk samples what happens naturally when thin films are made.

■ **ROBERT POOL**