vanni Fazio of the Center for Astrophysics, a key supporter of SIRTF. Pellerin, for his part, plans to start presenting Space Telescope, the Gamma Ray Observatory, AXAF, and SIRTF as a unified package, a complementary set of space observatories spanning a whole wavelength range.

Finally, the community has to have realistic expectations about what is possible. There is simply not enough money in the science agencies to do everything at once, not when astronomy has to compete with geophysics, science education, and all the rest.

This is admittedly frustrating, especially since scientists by their nature care passionately about their work—and especially since, as in the VLBA fight, the federal funding process so often results in cross-disciplinary priorities being set for ad hoc and political reasons.

On the other hand, there is no realistic hope of seeing the science budgets rise much in the foreseeable future. It might help, a little, if the scientific community could find some more systematic way of making those cross-disciplinary tradeoffs—perhaps as a Field Committee writ large.

But then, no one has yet found a good way to do that. As one veteran of the NASA adsvisory panels says, "You're asking for something that no human being can accomplish."

—M. MITCHELL WALDROP

Avoiding the Schistosome's Tricks

Using the newest methods of molecular immunology, researchers are learning to induce immunity to schistosomes

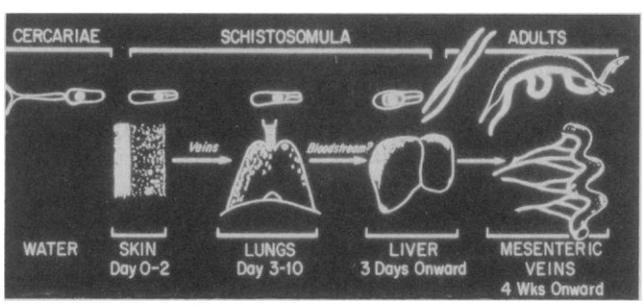
As far back as records of civilization go, there are descriptions of schistosomiasis. It is a disease that dates at least to 2000 B.C. in Egypt—the time of the pharaohs. There is even a hieroglyphic symbol for it, a penis dripping blood, which is a symptom of schistosomiasis. It is a disease that was so common in Egypt that blood in the urine was considered a puberty symbol for males. And it is a disease that even today afflicts 1 in 20 of the world's population—200 to 300 million people—in Africa, the Middle East, Central and South America, China, the Philippines, and Malaysia.

If ever an organism were well adapted to live in human hosts it is the schistosome, the worm that causes schistosomiasis. Once the schistosomes establish themselves, a person is literally defenseless against them. The immune system makes no headway whatsoever.

Like other parasitic diseases, schistosomiasis is now attracting the attention of molecular biologists and immunologists. Fascinated by the organism's ability to evade its host's immune system, investigators are searching for ways to trick the schistosomes and produce a vaccine against the disease. Their work has focused on monoclonal antibodies and anti-idiotype vaccines. Although no vaccine is imminent, all believe that one will come eventually. Because this research necessarily focuses on how the immune system is activated and inactivated, it is leading to new insights into control of immune reactions, including the isolation of substances that seemingly shut down portions of the immune system.

The current search for a schistosomiasis vaccine is only the latest in a long series of attempts to control this disease. From time to time, governments or organizations including the Rockefeller Foundation have made all-out efforts to eliminate the disease from certain parts of the world. Mao Tse-tung even tried to eradicate it from all of China and the Chinese today, disregarding patent rights, are manufacturing a new antischistosomiasis drug, praziquantel, and passing it out to their people. But none of these efforts has been completely successful. As Theodore Nash of the National Institute of Allergy and Infectious Diseases (NIAID) explains, "The problems with schistosomiasis are economic and political. If you had sewerage systems, if you had places to put feces, you wouldn't have schistosomiasis or you wouldn't have much."

The current best hope for stemming the disease is to use drugs and to try and prevent exposure. A number of public health experts are extremely enthusiastic about praziquantel, a drug that is effective against all species of schistosomes and is taken as a single dose. But praziquantel is expensive—it costs $30 per dose—and people, once cured, can be reinfected. Bayer, the drug's manufacturer is, however, selling the drug at cost, at $2 a dose, to Third World countries, in cooperation with the World Health Organization. Yet even $2 a dose is a lot of money for poorer countries. Moreover, if a country like Egypt spent $5 or $6 million on the drug to treat most of its infected people, the people would most likely have the disease again within the next few years unless exposure to the schistosomes can be prevented. And, of course, no drug is a panacea. As a drug is used more and more, it becomes increasingly likely that resistant strains of the organism will develop.



Life cycle of the schistosome

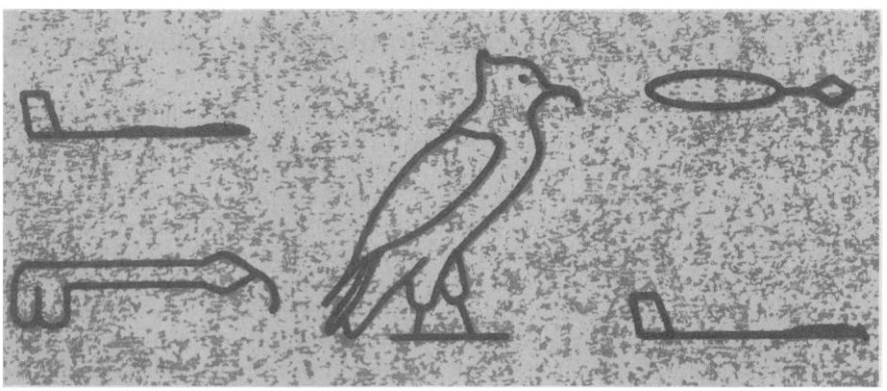
The worm, which does not multiply in its human host, can live for as long as 20 or 30 years. [Laboratory of Parasitic Diseases, NIH]

Like many other parasites, the schistosomes have a complex life cycle. Infected persons excrete the microscopic yellow schistosome eggs in their feces. If the feces get into freshwater, tiny embryos emerge from slits in the eggs and swim about rapidly until they find a snail host. The embryos develop and multiply in the snails, and, within a month or two, the snails start releasing thousands, or even tens of thousands of schistosome larvae per day.

The larvae home in on people who happen to be in the water, sensing people in some way that is not understood.

They burrow into an individual's skin, stay there for a day or two, and then enter the microcapillaries. The developing worms are swept by the blood stream to the person's lungs, where they stay for about 10 days. Then they travel through the vascular system to the hepatic portal veins which receive nutrients from the gut.

All this time, the worms have been differentiating into males and females. In the hepatic portal veins, the males and females find each other and mate. Then the joined males and females migrate to their final destination which, in the case of one species, *Schistosoma mansoni*, is the mesenteric veins of the upper intestine—the veins that feed the intestine. In another species, *S. japonicum*, the pairs go to the mesenteric veins of the lower intestine, while in a third species, *S. haematobium*, the destination is the veins of the bladder.



Schistosomiasis hieroglyphic

The schistosomiasis symbol, pronounced aaa, *is on the Ebers' papyrus of about 1500 B.C.* [*Fogarty International Center, NIH*]

Once settled in their final resting place, the male and female worms copulate for the rest of their lives, producing a steady stream of eggs. Each pair produces 300 to more than 3000 eggs per day and the worms may live for 20 to 30 years, although they more often live from 3 to 8 years.

About half of the eggs migrate through the wall of the intestine or, in the case of the *S. haematobium* species, the bladder, and the rest are swept with the blood to the liver where they cause a severe inflammatory reaction. The eggs that do get out to the intestine or bladder are excreted and are able to enter a new snail host.

Schistosomiasis patients frequently suffer intestinal upsets, such as vomiting and diarrhea. Later in the course of the disease, those infected with *S. mansoni* or *S. japonicum* develop liver damage and typically have huge, hard livers, like those seen in alcoholic cirrhosis. Those infected with *S. haematobium* have bladder damage and heavy bleeding into their urine. The cause of the pathology is the infected person's immune reaction to the worms' eggs. The effect is chronic illness and disability.

Ironically, although the worms are living in veins where they are fully exposed to the immune system, they are never attacked by it. The hope for a vaccine lies in the ability of the immune system, if properly stimulated, to prevent an infection in the first place. As Alan Sher of the NIAID remarks, "The immune system has no way of coping with a natural infection. There is no evidence of a natural immune response that will cure an ongoing infection. Basically, the immune system is powerless to cope once you have the infection and the immune system is in large part responsible for the disease."

But how do the worms evade the immune system? One of their tricks, apparently, is to coat themselves with the host's own antigens. In the late 1960's, Ronald Smithers and Roland Terry of the Medical Research Council in Mill Hill, England, discovered, to their surprise, that when mice and other laboratory animals are infected with schistosomes, the worms become coated with molecules of their host. Working with John Clegg, they went on to find that at least one type of host molecule that coats the worms is blood group antigens. Sher, who was then at Harvard Medical School, subsequently discovered that the schistosomes also pick up the major histocompatibility antigens which the immune system uses to distinguish self from nonself. The implication was that the coated schistosomes are disguised so that they look just like a part of the host's own body to the cells of the immune system. There is nothing foreign about their surfaces. "Wolves in sheep's clothing," Sher remarks.

As intriguing as this antigen coating was to the researchers, they soon discovered that it is not the whole story. Even if the hosts are made immune to a chemical on the surface of the worm, they cannot destroy the worms, as Gina Moser of Harvard Medical School and Sher demonstrated.

Smithers and his colleagues also find that young worms remain invulnerable to killing in vitro, even if they are stripped of their coating of host antigens. "We cannot destroy 4-day-old worms in the test tube with antibodies," Smithers says. Yet, "I still believe the adult worm is largely protected by host antigens."

One possibility is that if the worms do indeed produce substances that prevent the immune system from attacking them, these substances could be very useful drugs. An investigator who is actively looking for such substances is Andre Capron of the Institut Pasteur in Lille, France. Capron and his associates have isolated from the serum of infected rodents a variety of substances which, in vitro at least, suppress the immune system. These include a tripeptide, threonine-lysine-proline, that inhibits macrophages and that has great potential as an anti-inflammatory agent. Another substance secreted by the worms is a small molecule that selectively inhibits T cells. "It has the same type of activity as cyclosporine and it works on T-cell leukemias in the mouse, both in vitro and in vivo," Capron says.

With all this evidence that the schistosomes may be suppressing their host's immune system and that the host is incapable of killing at least the mature worms, prospects for a vaccine would seem quite bleak. But schistosomiasis investigators uniformly say that they believe there is a great deal of hope for a vaccine because, first, there are new data indicating that at least some people *can* become immune to the disease and, second, they are able to induce at least partial immunity in experimental animals.

The question of whether people ever become immune to schistosomiasis infections has long plagued researchers. The final encouraging answer that immunity is possible was recently announced by Anthony Butterworth of the University of Cambridge and his colleagues who conducted what Donald Harn of Harvard Medical School describes as "a very elaborate study" in the village of Ietune in Kenya. This is an area where 97 percent of the schoolchildren had severe schistosomiasis infections.

Butterworth's study was a long term one in which he and his associates first determined how much contact children

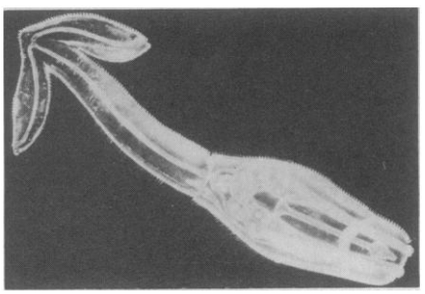
of different ages have with the water. To do this, the investigators recruited villagers to watch the stream and pools that are the town's water supplies and to determine contact minutes. They then selected 129 children, about half of whom had severe infections and little water contact—and were predicted to be vulnerable to schistosomiasis—and about half of whom had minor infections and a great deal of water contact. The second group were predicted to be immune to the disease.

The next step was to treat the children with oxamniquine. It cured 70 percent of them. Finally, they were followed to see whether they became reinfected when they were exposed to the snail-infested waters again. More than half of them were not reinfected. The study, says Harn, means that "for all of us working toward the production of a defined vaccine, there is hope."

The way most researchers are going about developing vaccines is to make monoclonal antibodies to the organisms and then to show that these antibodies can confer immunity to mice. This is the approach of Clegg, Harn, Adel Mahmoud of Case Western University, Capron, and Michael Phillips of the University of Pennsylvania School of Medicine, for example. Harn and his associates have also succeeded in isolating the antigen that their monoclonal antibodies recognize and are using that to immunize. And now, John Clegg and Maire Smith of Wellcome Laboratories have used a purified antigen to immunize monkeys against schistosomiasis. Harn, who hails this work, remarks, "To immunize mice is one thing. But to immunize a monkey with a pure antigen is fantastic."

Now that they have monoclonal antibodies, the investigators are able to try all sorts of sophisticated molecular manipulations. One thing they all are doing is to try to clone the genes for the antigens the antibodies recognize. Another is to make "anti-idiotype" antibodies.

One theory of how the immune system regulates itself is that it makes antibodies to its own antibodies, thus tuning down immune responses. These anti-idiotype antibodies are postulated to regulate the immune response to a given antigen by binding to T cells, which may have similar receptors for the antigen. They are then thought to stop the T cells from stimulating antibody production. To produce anti-idiotype antibodies, investigators have immunized animals with monoclonal antibodies which recognize schistosome eggs or surface membrane antigens. The result is an antibody to the



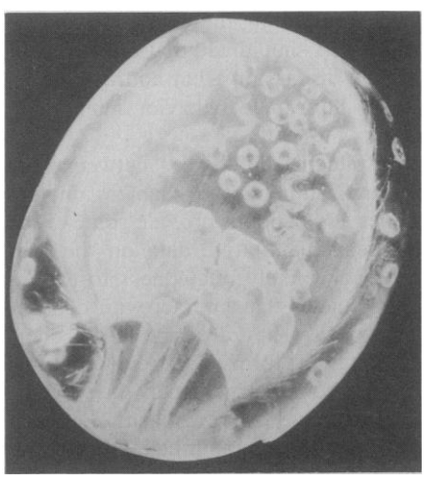
Schistosome larvae

The larvae, released in water by snails, burrow into the skin of people in the water. [Laboratory of Parasitic Diseases, NIH]

monoclonal antibody, or an anti-idiotype antibody. "The reason this is important is not that it is unique or unexpected," says Phillips. "But it is important because it shows the tremendous biological relevance of anti-idiotype antibodies."

With anti-idiotype antibodies, researchers can ask whether the original antibody appears naturally in animals during infection. Harn finds that it does. Then they can ask whether a similar antibody is made by humans with schistosomiasis. And, finally, anti-idiotype antibodies can themselves be used to vaccinate against schistosomiasis. Antibodies to anti-idiotype antibodies mimic the original antigen and result in an immune response to it. With an anti-idiotype antibody vaccine, says Harn, "You can make antibodies against a parasite without ever seeing the parasite antigen."

But promising as the work with monoclonal antibodies is, it is limited. The animals are never fully protected against schistosomiasis—the usual figure is that they are only 40 percent protected although a few researchers, Capron included, are claiming up to 70 percent protection in rats. Forty percent protection means that 60 percent of the worms that would ordinarily take up residence in a newly infected animal are unharmed by the monoclonal antibodies. "This is the great problem with a schistosomiasis vaccine," says Clegg. "People have moved on to genetic engineering, but we still don't know how to use the antigens in a vaccine. The problem is to find the correct immune response that you must generate."



Egg of a schistosome

The yellowish eggs are excreted by infected persons and the tiny embryos inside escape and enter snails. [Laboratory of Parasitic Diseases, NIH]

Stephanie James of George Washington University School of Medicine and Sher believe that the important immune response does not even involve antibodies. After 4 years of work and 20,000 mice, James established that one mechanism of immunity to schistosomiasis in mice involves T lymphocytes, macrophage activation, and delayed hypersensitivity. Then James discovered that the way to induce delayed hypersensitivity is to give mice parasite antigens together with an adjuvant, one of a group of substances that stimulate the cellular immune system, and to inject the mixture into the skin. She and Sher report that mice injected in this way develop up to 70 percent protection against subsequent infection. James and Sher have tentatively identified a schistosome protein that seems to be responsible for inducing immunity in their system. "We may have gotten around the schistosome's tricks," says Sher. Mahmoud and his colleagues, working independently, have essentially the same results.

Of course, there still is a long way to go on vaccine development, but there are a few advantages to working with schistosomiasis. "A vaccine against schistosomiasis may be *easier* than a vaccine against malaria," Sher emphasizes. "With malaria, the parasites multiply in the host so you need a heavy immunity to keep them down. Schistosomes don't divide in their host, so if you knock off 60 to 70 percent of them, you will reduce the worm burden so the disease is negligible. It doesn't have to be a sterilizing immunity."

So the researchers are hopeful. "Call it my optimism, call it my faith in what science has accomplished in the past, but I think we will develop a vaccine," says Phillips. Still, Mahmoud sighs, "it's going to be a long story."—GINA KOLATA

Additional Readings

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