while a step in the right direction—would need to be 10 times larger to make a real impact. "Why do the research if you aren't going to do the development?" he asks.

So far, however, there's no evidence that the other major funders are simply going to mimic TDR's policies. "Our institute still very much emphasizes basic research," says Stephanie James, chief of the parasitology and tropical diseases branch of NIAID. But given the continuing pressure on parasitology funding agencies to prove that they're giving good value for money, the fears for the future of basic parasitology research do seem justified. "We don't have the time or the resources to take a laissez-faire, undirected research approach," says Denis Prager, who heads the MacArthur Foundation's health program.

Researchers and policymakers from both sides of this debate are now hoping that a study being conducted under the aegis of WHO will resolve these arguments. The Ad Hoc Health Research and Development Review, which will report in fall 1995, is building from last year's World Development Report from the World Bank, which rated the economic impact of the various diseases (*Science*, 9 July 1993, p. 155). The review, says its chair, health economist Dean Jamison of the University of California, Los Angeles, will for the first time produce a detailed menu of priorities—estimating the long-term gains that can be expected from investing $10 million in drug development for disease X, $20 million in basic immunology for disease Y, and so on. Moreover, the report should also point out the mismatches between the current international portfolio of research and the true health needs of developing countries.

But for parasitologists, the big question is whether the review can do anything to improve their discipline's dismal funding situation. So far, the answer is not clear, and some researchers fear it could squeeze budgets for parasitology even further if the final report suggested putting more money into researching remedies that are applicable in a developing country setting for, say, cardiovascular disease—which poses major health problems in the Third World as well as the industrialized north.

Nevertheless, Jamison is optimistic that the overwhelming take-home message from the review will be the strong case for investing more in all kinds of health research as a means to promote countries' economic development. What's needed, he says, is a move away from "the zero-sum environment." If that happens, he says, funding for parasitology should not be threatened. Thousands of parasitologists—and, more importantly, countless millions of people suffering from the debilitating effects of parasitic disease—hope Jamison's optimism is well-founded.

–**Peter Aldhous**

PARASITE CONTROL

Finding 'Sustainable' Ways to Prevent Parasitic Diseases

Back in the 1950s, public health workers thought they were well on their way to wiping out not only malaria but also many of the other half-dozen or so major parasitic diseases that afflict humankind: By spraying DDT or other pesticides, they expected to kill the "vectors" (usually insects such as the malaria-carrying *Anopheles* mosquito) that transmit the parasites to their human hosts. For malaria, they had another weapon as well, chloroquine, a cheap, safe drug that prevents the disease from developing in people who do get infected. As is obvious today, however, that early optimism proved unfounded. Not only did the *Anopheles* mosquito rapidly become resistant to DDT, but the malaria parasite itself became resistant to chloroquine. Today, World Health Organization (WHO) experts estimate that the number of infected people worldwide is rising at the rate of about 5% annually.

But scientists don't give in, and the new buzz word is "sustainability." Says Hans Remme, who coordinates applied field research for the Special Program for Research and Training in Tropical Diseases (TDR) in Geneva, a joint effort of WHO, the World Bank, and the United Nations Development Program: "Any attempt at a short, rapid solution for these chronic disease problems is not likely to meet with much success. Sustainability is what we are after."

What he means is that the parasitology community, having largely given up on widespread pesticide application, is looking to develop natural and low-tech adversaries to parasites. Yes, pesticides may be used, but only in a limited fashion—say, in those areas of individual homes where parasite-carrying insects are likely to breed. But researchers are looking elsewhere for their main lines of defense against parasites.

One common low-tech strategy under exploration uses simple mechanical methods to keep parasite-transmitting insects from infecting their human hosts. Because most of the 600 million cases of parasitic disease occur in developing countries where there is little money to spend on health needs, these have to be as cheap and easy to use as possible: T-shirts for filtering contaminated water, for example, or insecticide-impregnated bed nets to protect against mosquitoes. At the same time, public health workers are looking at how cultural and social practices influence the willingness of populations to undertake such parasite control methods (see box on p. 1860).

Biological controls—bacteria, plants, and fish that may be able to keep vector populations in check—are also coming in for a lot of attention. The advantage of biological controls over pesticides is described by Robert Gwadz, a malaria expert at the National Institute of Allergy and Infectious Diseases: "A good biological control should not threaten the environment and should persist beyond a single season." The problem is that the biological control strategy is not easy to implement. "If it were," says Gwadz, "someone would've done it a long time ago."

One success story. Indeed, the mechanical control strategies are the most advanced, already undergoing considerable

SOME "SUSTAINABLE" PARASITE-CONTROL OPTIONS

Disease	People Infected	Vector	Interventions
Chagas' Disease	18 million	Triatomid bugs	Plastering adobe walls Pesticide-impregnated curtains
Filariasis	90 million	Mosquitoes, black flies, mites	Styrofoam beads in latrines Medicated salt
Guinea Worm Disease (Dracunculiasis)	250,000	Water fleas	Cloth water filters Bore-hole wells
Leishmaniasis	12 million	Sand flies	Toxic plants
Malaria	270 million	Mosquitoes	Pesticide-impregnated bed nets
Schistosomiasis (Bilharzia, Snail Fever)	200 million	Snails	Predatory fish
Sleeping Sickness (Trypanosomiasis)	25,000	Tsetse fly	Odor-baited traps

Taking the Human Factor Into Account

Five years ago in Liberia, two researchers from the Johns Hopkins School of Hygiene and Public Health found what appeared to be a good way of keeping the population of malaria-transmitting mosquitoes in check: They showed that an edible African fish called *Tilapia nilotica*, which feeds on mosquito larvae, combined with bacteria that produce a larva-killing toxin, dramatically reduced the number of the mosquito larvae in experimental rice paddies. But, sadly, they were never able to put their control strategy to the test.

In 1989, a bloody civil war flared up in Liberia. A side effect was that one of the two researchers, Liberian Fatorma Bolay, had to sit idle in Monrovia, the nation's capital, while the other, the United States' Milan Trpis, shifted his research interests to a different parasitic disease, onchocerciasis, and to a different country, the Ivory Coast. The plight of that Liberian malaria-control project dramatically highlights one of the most important—yet most overlooked—factors affecting whether or not a parasite-control effort will succeed: human behavior.

Parasitologists and public health workers are currently exploring several ways to prevent parasitic diseases (see main story). But even the simplest and cheapest methods won't be used unless they fit in with the cultural practices of the population where they are being applied. "Behavior comes into play very strongly over the long term," says Hans Remme, coordinator for applied field research with the Special Program for Research and Training in Tropical Diseases (TDR) in Geneva.

Remme could be thinking of the uncertain prognosis for insecticide-treated bed nets—a staple of malaria control efforts in many parts of the world—in some parts of Africa. While the nets were easily accepted by people in the rice-growing areas of Mali where it's long been a tradition to give bed nets to newborn babies, the Fula of Gambia have been reluctant to use bed nets of any type. In fact, almost 40% of this group declined the pesticide-treated nets distributed during a large trial conducted by the Medical Research Council Laboratories in 1993. Why? The Fula's nomadic lifestyle doesn't lend itself to transporting nets and, because other ethnic groups believe the Fula are responsible for spreading malaria, they may have thought they were being unfairly singled out when asked to participate in the program.

And then there's gender. Carol Vlassoff, a social scientist at the World Health Organization (WHO), says: "Tropical medicine has almost completely ignored gender issues. Women are not consulted about control design, even though in many cases women are the very people who are actually going to be using these things." The result becomes clear in a recent study conducted by Peter Winch of the Johns Hopkins School of Hygiene and Public Health, Linda Lloyd, a public health consultant in San Diego, and their colleagues. The team found that women living in cultures that traditionally permit them little contact with males other than those of their own families—Indian women in purdah, for example—are often disturbed when strange males enter their homes to carry out vector control. They'll even bar the men from entering areas like the bedroom to set up nets or spray pesticides.

But cultural issues also offer opportunities: When Indian government officials first tried to get people in India to take diethylcarbamazine citrate (DEC), a drug used to treat filariasis, they encountered limited success. People were reluctant to take DEC for a variety of reasons, including side effects from the dosages found in DEC tablets and their distrust of government-run drug distribution, says C. P. Ramachandran, a filariasis expert with WHO. To get around the dosage problem, WHO recommended a strategy originally used to combat filariasis in some parts of China: mixing small amounts of DEC with table salt. "There's no odor, no taste," Ramachandran explains. "You don't even know you're taking a drug."

To further ease Indians' suspicions, the Indian government allowed the medicated salt to be commercially produced and sold, with DEC clearly marked on the label, at the same stores where people buy their regular food supplies. Sales of the medicated salt began only this May in Kerala, and it's still too soon to tell how effective the filariasis control project will be, but early sales figures look encouraging, Ramachandran says. Culture, it turns out, cuts both ways.

–R.K.

testing in the field. Take the T-shirt gambit, which is part of what appears to be the most successful effort in the long and frustrating history of parasite control: WHO's program to eradicate Guinea worm disease. The Guinea worm, *Dracunculus medinensis*, is found mainly in Africa, the Middle East, Pakistan, and India. And although infection with the parasite rarely kills people directly, many are disabled or die of secondary infections acquired when the female worms make their slow, painful exit from the body, usually by boring through the lower limbs.

Because people get infected when they drink water contaminated with the *Cyclops* water fleas that carry the Guinea worm larvae, the WHO eradication campaign centers on convincing each household to filter water drawn from shallow wells or surface water where the fleas live. The filter? Pieces of nylon gauze, distributed free of charge by Global 2000, a private health and development agency based in Atlanta. But Global 2000 epidemiologist Ernesto Ruiz points out that even simpler alternatives can work: "You can use a T-shirt or any other tightly woven cotton cloth that's available."

Combined with other control strategies, including targeted use of the flea-killing insecticide temephos and a public education campaign to encourage infected people to seek medical treatment and stay out of water sources when the female worms are leaving the body, this low-tech global thrust against Guinea worm disease has resulted in a dramatic drop in the number of cases: Less than 250,000 were reported in 18 participating nations in Africa and Asia in 1993, compared with an estimated 10 million to 15 million annually a decade ago. "Most people now are certainly confident...that we will eliminate Guinea worm," declares Don Hopkins, a health consultant for Global 2000. "The only question is whether we will make our December 1995 goal."

If only the malaria control program via mechanical means were going as smoothly. In particular, the widespread and well-known bed nets program has failed to impress many experts. The idea, notes John Sexton, an entomologist with the Centers for Disease Control (CDC) in Atlanta, is simple: Because *Anopheles* mosquitoes bite mainly at night, it should be possible to protect people with bed nets treated with pyrethroid insecticides that quickly kill mosquitoes in doses that are not toxic to humans. At an average cost of $3 to $4 each, bed nets are easily affordable in the developing world. Indeed, China has distributed 2 million nets annually since 1987, and UNICEF has directly supplied, or assisted local governments in providing, tens of thousands in Africa and Southeast Asia.

So what's the problem? Some public health officials are concerned by the inconsistent results with bed nets obtained in the field. For example, in a study of 73 villages in The Gambia, a team headed by Brian Greenwood of the Medical Research Council Unit in Fajara, The Gambia, found that use of treated bed nets was associated with a 63% reduction in overall mortality among children ages 1 through 4. But a recent study conducted in southeast Asia by the Shoklo Malaria Research Unit in Thailand failed to reproduce the African success. There was only a "marginal" effect on the number of malaria parasites in the women's bloodstreams, although they did show a reduction in malarial anemia.

Bed nets' apparent failure under certain circumstances is baffling to many researchers. But work by John Beier, an infectious disease expert at the Johns Hopkins School of Hygiene and Public Health, suggests that the use of bed nets may be pointless unless they keep out each and every mosquito.

And then there's evidence developed by a U.S.-Kenyan team led by J. M. Vulule of the Kenya Medical Research Institute in Nairobi and Raymond Beach of the CDC that the pyrethroids used to treat bed nets may be inducing resistance in *Anopheles* mosquitoes just as DDT did. Specifically, they found resistance to the pyrethroids among *Anopheles gambiae* mosquitoes exposed to permethin-impregnated bed nets and curtains in four villages near Kisumu, Kenya.

It's no surprise, then, that a debate has broken out among experts over what to do. Beier, among others, has concluded that "wide-scale distribution of bed nets is not a great thing to do right now. It could be a waste of money and public health resources." But Rangit Atapattu, a health adviser with UNICEF, who saw many children stricken by malaria while practicing medicine in his native Sri Lanka, disagrees. "We are responding to a demand from the field," says Atapattu. "Bed nets are not the answer to all the problems with malaria, but their critics don't have ready another answer. Today, malaria is the number one killer of children under 5 in sub-Saharan Africa. You have to do something now."

Indeed, even the successful Guinea worm program is not without potential problems. Like most other strategies that rely primarily on mechanical means to prevent parasitic diseases, it requires considerable human labor and perseverance to be effective over the long term. That's why public health workers are looking to biological controls—ranging from bacteria to fish and ducks—as a possible way of providing more enduring methods of parasite control.


WHO/TDR/WELLCOME

Targeted. Biological controls are being sought for schistosome parasites.

One of the most active areas of biological control research involves efforts to find new ways to combat schistosomiasis. Also called bilharzia or "snail fever," schistosomiasis is, after malaria, the second most common lethal parasitic infection, afflicting 200 million people. The disease is caused by waterborne *Schistosoma* blood flukes (a type of flatworm) that develop in certain species of snails and then exit the snails to infect humans by burrowing through their skin while they are wading or swimming. Once inside a human, the worms mature in the blood vessels and then produce eggs, which can be life-threatening when they are trapped in the liver, bladder, brain, or other vital organs.

Snail-eating fish shows promise. Perhaps the most promising of the biological controls being tested for schistosomiasis is a snail-eating fish called *Trenatocranus placadon*. Africa's Lake Malawi was considered relatively free of schistosomes until 1992, when the disease began to appear. In a joint effort, Martin Cetron, an epidemiologist with the CDC, and Jay Stauffer, an ichthyologist at Pennsylvania State University, noted that the appearance of schistosomiasis around Lake Malawi coincided with the decline of *T. placadon* populations, apparently the result of overfishing.


MARK EDWARDS/WHO/TDR

Under wraps. Pesticide-impregnated bed nets are being used for malaria control.

Subsequent tests in aquaculture confirmed, Stauffer says, that the half-foot-long fish is able to keep in check populations of a snail species that serves as an intermediate host of *Schistosoma haematobium*. This suggests that it might be possible to reduce schistosomiasis infections by restocking Lake Malawi with *T. placadon*. Stauffer says that action is now being considered, and talks are under way with local village people about how to prevent overfishing if the *T. placadon* population is replenished.

In other cases, researchers are looking for plants that can serve as biological controls. One example involves leishmaniasis, a disfiguring disorder spread by sand flies and seen mostly in the Middle East, Northern India, Pakistan, parts of Africa, and in Latin America. Noting that the protozoan *Leishmania* parasites reside in the sand fly gut, parasitologist Yosef Schlein at Hebrew University's Hadassah Medical School in Jerusalem is trying to determine whether certain types of vegetation consumed by sand flies might kill the parasite and therefore help prevent its spread to humans.

Early results suggest that this might be the case. Schlein's team found a high rate of *Leishmania* mortality in sand flies fed in the lab on *Ricinus communis*, the poisonous castor bean which grows in arid areas in the Middle East and elsewhere. In preliminary field studies, Schlein found that the *Leishmania* mortality rate was about 20% in infected flies collected from arid areas, compared with a mortality rate close to zero among flies caught in irrigated regions. If further work confirms that the higher parasite mortality in the arid areas is in fact due to sand flies eating *Ricinus* or other poisonous plants that grow there, it might be possible to reduce leishmaniasis by planting the toxic vegetation in residential areas.

High hopes, but the key to successfully instituting biological controls, as these examples suggest, will be a careful knowledge of the habits of parasites and their vectors, coupled with the ability to tailor the controls to specific locations. Since this may prove as difficult in its own way as devising a regimen of effective mechanical approaches, most parasitologists believe that, in the final analysis, no strategy—be it pharmaceutical, mechanical, or biological—will single-handedly control the many parasites afflicting humankind today. The parasites themselves are so wily and the social realities, including poverty and lack of education, so formidable, that only a multipronged attack is likely to get parasitic diseases to relax their deadly and disabling grip on humanity. The scientific and public health communities, it seems, have their work cut out for them.

–Rebecca Kolberg

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Additional Readings

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