# Fighting Parasites on a Shoestring

Desperately short of cash, some funding agencies are focusing on applied research to develop drugs and vaccines—much to the alarm of basic researchers

The acronym sported by the U.S. Agency for International Development is AID, but far from aiding Michael Alpers, director of the Papua New Guinea Institute of Medical Research, in his contribution to the global battle against malaria, AID has pulled the rug out from under him. After funding the Australian epidemiologist to the tune of $5 million over 7 years—a period spent building from scratch the infrastructure needed to test desperately needed vaccines in the field—AID officials stunned Alpers a few months ago when they told him the agency would stop supporting his project at the end of June. By then, Alpers and his local field assistants would have been gearing up to begin clinical trials of candidate malaria vaccines. Instead, they will be frantically scrambling for funds to keep the project alive. "We at least would have assumed that they would have honored their already-established commitment," says an incredulous Alpers, whose grant was not due for renewal until March 1995.

WHO/TDR/LSTM

**By air...** *Anopheles* mosquitoes like this one transmit the most common parasitic disease, malaria.

Alpers' case is extreme—but it illustrates perfectly the precarious nature of parasitology funding. In AID's case, savage budget cuts, caused by the tough Clinton budget, have forced the agency to slash its malaria vaccine program in half this year. But the problem is a generic one, largely because parasitic diseases are mainly a problem in the Third World. There they cause more than a million deaths each year, with childhood malaria alone accounting for around half that figure. But the countries most affected spend few of their scarce dollars on research—indeed, they provide only about 2% of the world's total health research funding. That leaves parasitology at the mercy of funders in the industrialized world. And it is no surprise that parasites fall low on the industrialized world's list of medical research priorities. So despite good progress in basic research, Ruth Nussenzweig, a leading malaria researcher at New York University School of Medicine, says "the field is terribly underfunded, and it's going through a crisis." And that crisis is causing a bout of soul-searching about the discipline's future that is generating widespread unease among bench researchers.

**SPECIAL NEWS REPORT**

In this issue on parasitology, *Science*'s News Department takes a look at some of the major issues the field is facing. The story on this page explores the soul-searching about research priorities triggered by the current funding crunch, while the following story looks at efforts to develop "sustainable" parasite-control strategies. The special news section is rounded off by a look at how mathematical modeling may help those control efforts. Policy Forums, Perspectives, and Articles follow.

These are the issues that cause parasitologists to blanch: First, granting agencies are increasingly being pressured to move away from a policy of simply funding the best proposals that come in. Why? Because, in a world of funding famine, a more directed approach aimed at developing specific products such as malaria drugs and vaccines may promise more bang to the buck and so be easier to sell to politicians and the boards of foundations. Second, researchers in developing countries are feeling increasingly threatened by the concern within the parasitology research establishment that the millions of dollars spent trying to build up parasitology research there may not have a high enough payoff. And third, some policymakers are questioning whether the overall international portfolio of research on tropical parasites matches the world's true health needs. For example, would it be better to shift funds from research on, say, sleeping sickness to malaria, which kills 15 times as many people? "If we don't have enough money to go round," says Joseph Cook, director of the tropical disease program run by the New York–based Edna McConnell Clark Foundation, "we'd better make sure that we spend it effectively."

WHO/TDR

**...And by water.** Snails serve as intermediate hosts for schistosome parasites.

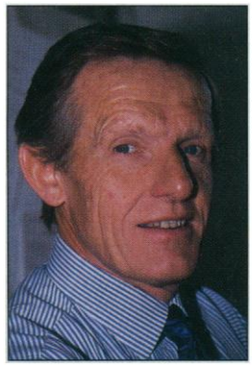
Not that all of this is entirely new. Tropical parasitology always enters the funding doldrums when the industrialized countries hit the economic skids. That's when foreign aid budgets—which have long been a significant source of funding for parasitology—inevitably get squeezed. But this time, the problem has been compounded by the decisions of two major U.S. foundations that have provided generous support for the discipline to scale back their activities. The Rockefeller Foundation, which in the late 1970s stimulated the field with a high-profile program on "great neglected diseases," has already all but left the field. And the MacArthur Foundation, which has invested around $50 million in molecular parasitology over the past decade, intends to wind down its program, with the probable exception of its effort to engineer the insects that transmit parasites so that they can no longer spread disease (*Science*, 30 July 1993, p. 546).

Adding to the field's miseries, the current 2-year budget of the leading international agency funding research in tropical parasitology, the Geneva-based Special Program for Research and Training in Tropical Diseases (TDR), is down 6% from 1992–93 to $66.6 million for 1994–95, largely because that agency relies for funding on donations provided mostly through governments' foreign aid spending. While that decrease appears modest, TDR—which is run by the United Nations Development Program, the World Bank, and the World Health Organization (WHO)—is also shifting its priorities, putting greater emphasis on field studies to test parasite-control strategies as well as its drug development program.

The shift is understandable in one regard. Few researchers would dispute that the field of parasitology has

a disappointing record in converting cutting-edge molecular science into new drugs and vaccines. In terms of antimalarial products, says malariologist Louis Miller of the National Institute of Allergy and Infectious Diseases (NIAID) in Bethesda, Maryland, "what we have is pretty lousy." And with drug-resistant forms of the disease becoming a major concern, he says, finding new antimalarials is a top priority.

One major difficulty is the attitude of the pharmaceutical industry, which has been beating a steady retreat from the development of antiparasitic products. As the costs of bringing a new drug to the market have spiraled upwards, companies have become less willing to invest in diseases of poverty, where there is little prospect of large profits. Take the London-based Wellcome drug company: In 1982, the firm had a team of 50 people working to develop drugs against a wide range of human and animal parasites. But since then, says Win Gutteridge, Wellcome's head of antiparasite research, diseases have "gradually got picked off, one by one." By 1996, he says, the company should register a new antimalarial drug, "but that will probably be the end of Wellcome's activities."



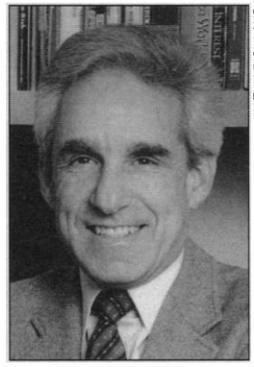
ANDY CRUMP/WHO/TDR

**Shifting priorities.** TDR's Tore Godal.

To help take up the drug development slack, TDR set up a product development unit in 1991, and today, almost half of the $21 million the agency allocates to research is spent on drug and vaccine development projects. "We cannot continue just to fund basic research and assume that product development...will occur automatically," says TDR director Tore Godal.

But TDR cannot bear the multimillion-dollar cost of developing a new drug from scratch. Instead, its main strategy is to screen for antiparasitic activity among drugs that have been developed for other purposes. This strategy may bring some good news for sufferers of parasitic disease: Having signed a screening contract with the Belgian company Janssen Pharmaceutica to bolster its overworked network of academic screening labs, the agency should soon be testing several thousand new compounds a year. When promising drugs are identified, TDR will finance and run the clinical trials that would usually be the responsibility of a drug company (see Policy Forum by Godal on p. 1864). But TDR's move into product development, coupled with the fact that it has increased its budget for field research to test the effectiveness of existing disease control strategies, is putting pressure on many of TDR's other activities.

One such area is research by scientists in developing countries. Everyone agrees that it's important to integrate Third World scientists into the international research effort. The argument runs that Third World scientists, with their intimate knowledge of the problems caused by the diseases, may be better placed to decide research priorities than their developed-world counterparts. Indeed, the European Union's $12-million-a-year effort on health research for developing countries makes it mandatory for the networks of labs applying for funding to include both European and developing-country partners. But when an agency like TDR comes under budgetary pressure, there are always some scientists who point out that much of the work could be done more efficiently in the more industrialized countries of the north.



KATHY RICHLAND

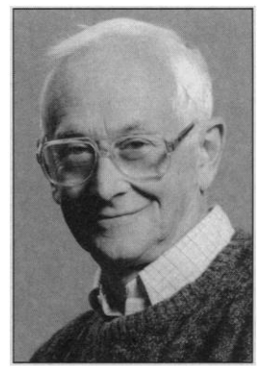
**No laissez faire.** MacArthur's Denis Prager.

TDR has responded to these concerns by keeping its level of support for developing-country researchers constant—at around 25% of its budget—while making Third World scientists a major focus for its push in applied field research. The result, says Godal, is that TDR will in future support much less high-tech molecular biology in the developing world, and what it does support will be mostly in more advanced countries like Brazil and China. And despite some complaints that the Third World is being left with the unglamorous end of the research spectrum, most developing-country scientists accept the logic. "Just pouring money into the south is not enough," says malariologist Kamini Mendis of the University of Colombo in Sri Lanka, who believes it's right to focus spending in developing countries on field projects that simply can't be done in the north.

But there have been loud cries of anguish about TDR's future direction, and the loudest of all come not from the developing world but from northern researchers working on basic biomedical aspects of parasitology, who fear that the stress on product development will squeeze TDR's support for fundamental science. Anthony Butterworth of the University of Cambridge works on both lab- and field-based projects looking at the human immune response to the liver flukes that cause schistosomiasis—information that might be useful for vaccine development. Says Butterworth: "I think they have gone over the top....There is still a need for more basic biology."

Other researchers are particularly concerned that TDR has over the past year started to target its budget for basic science onto a limited number of priority areas. Microbial geneticist Barry Bloom of New York's Albert Einstein College of Medicine, who chairs TDR's scientific and technical advisory committee, frankly acknowledges that, in the past, "we have tried to do a little bit of everything." But limited resources have now made that approach untenable, he says, so that it is necessary to focus on areas that may underpin the next generation of product development work—such as mapping parasite genomes and exploring how some of the immune system regulators secreted by mammalian cells seem to protect against parasitic infections whereas others actually increase disease susceptibility.

The concern among bench scientists, however, is that this more directed approach will ignore innovative new ideas. John David of the Harvard School of Public Health, who works on the immunology of schistosomiasis and the protozoan disease leishmaniasis, points to the work of his Harvard colleague Richard Titus, who has shown that a protein in the saliva of the sand flies that spread leishmaniasis greatly enhances the *Leishmania* parasite's ability to infect a new host (*Science*, 11 March 1988, p. 1306). This work has led to efforts to develop a vaccine against the protein that could block disease transmission. But, says David, it "came from basic research and not at all from a plan."



HARVARD

**Bench view.** Harvard's John David.

Still, the intense response to TDR's shifting priorities seems surprising given that the agency accounts for only a small proportion of total international funding for tropical parasitology; the extramural spending of NIAID alone, at over $40 million a year, outstrips TDR's total research budget. The reason, explains molecular biologist Luiz Pereira da Silva, who heads a lab working on malaria vaccines at the Pasteur Institute in Paris, is that TDR is a trend-setting agency that exerts "a kind of a psychological guidance on what's happening" elsewhere in the field. Moreover, some observers are calling for other agencies to follow TDR's move into the product development arena. Wellcome's Gutteridge, for example, argues that TDR's product development unit—

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<br>Pesticide-impregnated curtains |
| Filariasis | 90 million | Mosquitoes, black flies, mites | Styrofoam beads in latrines<br>Medicated salt |
| Guinea Worm Disease (Dracunculiasis) | 250,000 | Water fleas | Cloth water filters<br>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 |