Malaria Vaccine Raises a Dilemma

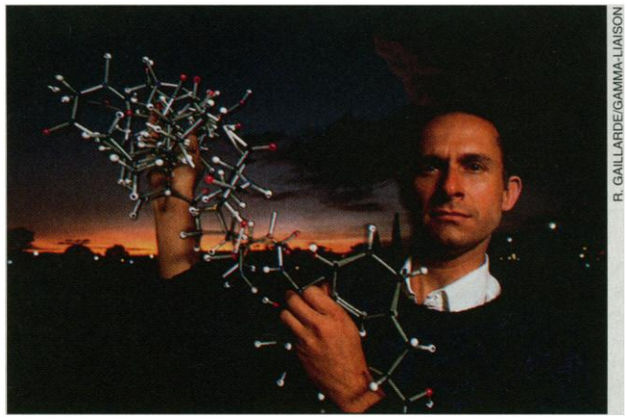
Colombian scientist Manuel Patarroyo has developed possibly the first effective malaria vaccine and wants the world's 300 million sufferers to receive it. But other malaria researchers say "not so fast"

GENEVA—Only very rarely does a scientist win the fame and adoration currently enjoyed by Colombian physician and chemist Manuel Elkin Patarroyo, inventor of the first malaria vaccine—known as SPf66—to show some efficacy in field trials. The shelves of his office are sagging with prizes—53 at the last count—most of them from Latin American organizations, but in the past 9 months he has added three European science awards and was voted "Doctor of the Year" in two polls of French physicians. In Colombia he is a national hero, and the personal endorsement of the president ensures that he is never wanting for research funds. His fans come from all levels of society: A couple of months ago, while he was supervising trials in the village of Chilvi on Colombia's Pacific coast, a group of children came up to Patarroyo and presented him with a piece of corn bread on which they had sculpted the letters "SPf66."

Such adulation is not surprising when you consider that Patarroyo's vaccine could be one of the few effective weapons against a disease that is believed to affect more than 300 million people and to claim the lives of at least 1.5 million every year—1 million of them young children in Africa. But while Patarroyo brings hope to legions of sufferers, many of his fellow scientists are skeptical. Today, after 10 clinical trials involving some 30,000 volunteers in five countries (see table on p. 322), the one thing everybody agrees on is that SPf66 is a powerful stimulator of controversy.

Recent clinical trials of the vaccine have shown some promise. One trial, carried out by Patarroyo and his group in Colombia during 1990 and 1991, showed that the vaccine cut malaria episodes overall by 39% and first episodes by 34%. Researchers hoped for a definitive answer from another trial completed last year in Tanzania with 600 young children and conducted independently of Patarroyo. Because it was the first field trial to pit the vaccine against malaria in Africa, where the disease is most deeply entrenched, the results were eagerly awaited. Announced last October in *The Lancet*, they showed that SPf66 had cut the incidence of first episodes of malaria by 31% (*Science*, 4 November 1994, p. 724).

These results have split the malaria research community. Many of the dozens of scientists interviewed by *Science* say the results are of "marginal significance" and that more study is needed before a decision on widespread use of the vaccine can be made. Some scientists are clearly disappointed. "How is it," asks Pierre Druilhe of the Pasteur Institute in Paris, "that in the 8 years since we've known about this vaccine, the scientific community hasn't managed to come up with a study that can give us a clear answer to the question: Is it truly effective?" Druilhe's frustration stems partly from the fact that the number of malaria episodes in the Tanzania trial was low, and so the reliability of the 31% finding is open to question.



R. GAILLARDE/GAMMA-LIAISON

Injection of hope. Manuel Patarroyo holds a model of his vaccine, which consists of three peptides.

Patarroyo and his supporters, on the other hand, see the results as a green light. "Tanzania," he says, "was to be the ultimate test. It gave a result. Even at a modest 31% efficacy, this vaccine could help easily 100 million people. Let's use what we've got." Spanish epidemiologist Pedro Alonso, a member of the Tanzania trial team, becomes indignant at the thought of holding up application of the vaccine: "Try telling the villagers in Africa that they're going to have to wait while they watch their children die from malaria."

The dispute over the efficacy of the vaccine is, however, much more than a battle of percentages. On one level, the controversy and criticisms are scientific: Researchers have criticized the type of vaccine Patarroyo produced and how he produced it, and they have picked holes in his early trials. "Science attacked him destructively, not with the aim of helping him," says Peter Reeve, who heads product development at the Special Program for Research and Training in Tropical Diseases (TDR), based at the World Health Organization (WHO) in Geneva.

On another level, the controversy has a more personal edge. Patarroyo is freewheeling, flamboyant, quixotic, and mercurial, with a penchant for hyperbole—everything that the archetypal First-World scientist shies away from. He is also a researcher from a small developing country who has achieved fame without running the hierarchical, regulatory, financial, and peer-review gauntlet that scientists from most developed countries have to face. Patarroyo thinks there is more than a touch of jealousy behind "the bitter, aggressive reaction" of northern scientists to his vaccine. "I knew it would not be easy for people to swallow the fact that I had made the first chemically synthesized vaccine, the first vaccine against a parasitic disease, and the first vaccine against malaria."

Whatever continues to fuel the controversy, it is putting the world's health authorities and agencies in a difficult position. News of the Tanzania trial's results spread quickly to many of the 90 countries afflicted with malaria. "We have been showered with requests for our vaccine," says Patarroyo—at least 17 countries have placed orders. WHO, however, is counseling patience. In a press release issued in October, the UN agency said the Tanzania trial result "does not warrant widespread use of the vaccine at the present time." Further studies, WHO insists, are needed. But as countries rush to grab onto anything that may have some effect against malaria, WHO's caution may get trampled underfoot. In the words of one WHO insider, the agency is on the horns of "an unprecedented dilemma."

A wily foe

When Patarroyo—who studied virology at Yale University and immunology and biochemistry at Rockefeller University—chose to tackle malaria, he took on a task that had confounded many vaccine experts. The malaria parasite is a complex organism that is carried by mosquitoes and slips into the human bloodstream when the mosquito takes a blood meal. Inside the body the parasite grows

Just Sign on the Dotted Line

To give, the saying goes, is easier than to receive. But for Manuel Patarroyo and the World Health Organization (WHO), both are proving difficult. As a humanitarian gesture, Patarroyo announced in June 1993 that he intended to give the rights to distribute his SPf66 malaria vaccine to WHO. The organization has had donations of this kind before, including ivermectin, the anti–river blindness drug, and eflornithine, the anti–sleeping sickness drug, from two U.S. drug companies, but the offerings invariably come with strings attached. SPf66 is no different, and as three versions of a licensing agreement have crossed the Atlantic between Geneva and Bogotá over the past 18 months, relations between donor and recipient have become decidedly chilly.

WHO proposed an agreement that would give it the right to decide when the Colombian vaccine is ready for full-scale manufacture and to choose the manufacturer best able to provide a product of the highest quality at the lowest price. The manufacturer would sell the vaccine to developing countries at a "preferential" price for public-sector use and to commercial customers at whatever profit the market will bear.

Patarroyo refused to consider such an agreement and has more or less given WHO the cold shoulder since receiving the latest version last March. He finds it "insulting" that the agreement still calls his invention a "candidate vaccine" and would give WHO the sole right to decide when to go into large-scale production. Patarroyo also objects to WHO's retaining the right to choose who will manufacture the drug. "If our plant can make the vaccine as cheaply and to as high a quality as any other manufacturer, we should have first option to make it," he says. The Colombians insist that they are not looking to make money from the vaccine.

As *Science* went to press, the two sides had agreed to talk to each other again. But even if they can overcome their differences, for the Colombians there would still be something missing from the agreement—something intangible: "A symbolic, moral gesture on a par with the humanitarian generosity that this donation from the Colombian people represents," says Guillermo Alberto Gonzalez, Colombian ambassador to the United Nations. The Colombians estimate that the work on developing the vaccine over the past 20 years amounts to about $700 million.

A fitting response to this gesture, they suggest, would be for the donation to win Colombia a place among the select group of 12 donor members of the 30-member board governing the WHO-based Special Program for Research and Training in Tropical Diseases (TDR). These 12 nations are virtually permanent members of the board and are almost always developed countries. Not possible, says WHO: Membership of the TDR's board is subject to a constitutional election procedure that cannot be tinkered with to meet the demands of a single country.

At the end of this month a WHO lawyer and TDR malaria vaccine expert will fly to Bogotá to try to find "alternative options," as TDR Director Tore Godal puts it, that meet the Colombians' conditions. Patarroyo says the agreement must "recognize our gesture for its moral, humanitarian worth. I owe this to the Colombian people."

–J.M.

through many stages, eventually bursting open red blood cells and causing a disease typified by fever and other flulike symptoms. In the 1960s and '70s, the extensive use of drugs and insecticides, mainly DDT, wiped out malaria from most developed countries and loosened its hold on several areas of the developing world. But the disease was soon on the rebound as the mosquitoes evolved strains resistant to the insecticides and the parasite developed resistance to anti-malarial drugs.

Over the past 20 years, vaccine researchers have focused mainly on the early stages of the parasite after it enters the body in an attempt to block infection at the outset. Patarroyo, however, took a more difficult route: He designed a vaccine against the much more complex blood stages of the parasite—stopping disease, not infection. This approach raised eyebrows in the immunology community, as did his decision to make the vaccine entirely out of synthetic protein fragments, or peptides. At the time, peptides were thought capable of stimulating only one arm of the immune system, the antibody-producing B cells, whereas the prevailing wisdom required T cells as well in order to achieve protective immunity.

Skeptics also pounced on the elaborate and painstaking process of elimination Patarroyo used to find the right peptides. He took 22 "immunologically interesting" proteins from the malaria parasite—identified using antibodies from people immune to malaria—and injected these antigens into monkeys and found four that provided some protection against malaria. Patarroyo then sequenced these four antigens and chemically reconstructed dozens of short fragments of them. Again using monkeys—more than 1000 of them obtained cheaply from the Colombian rain forest—he tested these peptides, individually and in combination, until he hit the jackpot: a combination of three peptides he dubbed SPf66.

When Patarroyo announced in 1987 that he had produced a vaccine, few took him seriously. Northern scientists nodded sagely as the vaccine's efficacy rate in trials steadily slid downward from an early high of 82%. Some of the early skepticism has been dispelled by later studies: The vaccine has been shown to stimulate T cells, and the antibodies it induces do recognize real malaria parasites rather than just the vaccine's peptides. But some significant unknowns remain: Only one of SPf66's three main antigens has been fully identified as belonging to a blood-stage form of the malaria parasite, and no one yet knows if the vaccine can be manufactured reliably in large quantities.

In the end, however, it is the vaccine's performance in clinical trials in humans that is the key, but here too its track record is mixed. Paul-Henri Lambert, chief of WHO's vaccine research and development unit, sums up the reaction of many scientists to the Tanzania results: "A 31% rate is in a gray zone, at the limit of ineffectiveness. Within this zone, things become a matter of opinion, of philosophy." Roy Widdus, a vaccine expert with the U.S. Public Health Service, agrees: At a 31% level of protection "you will not reduce transmission of the disease to a significant extent—it'll be a bit like treatment, with the disease as a public-health problem just going on as usual." And malaria vaccine researcher Ripley Ballou of the Walter Reed Army Institute of Research in Washington, D.C., says the Tanzania study showed "no evidence of a reduction in anemia, which is a major consequence of malaria morbidity, and no statistically significant reduction in deaths. So, OK, we are measuring an effect, but of what consequence?"

But TDR Director Tore Godal is more upbeat. The findings of the Tanzanian and Colombian studies, he says, "show a clear consistency." The trials were also conducted in two entirely different situations—low-transmission Colombia and high-transmission Tanzania—with a different set of parasite strains in each. This suggests that the vaccine may be effective in widely differing malaria settings, he says. All in all, Godal "is convinced that the vaccine has shown true if limited efficacy in these studies. But I don't know what that means in a real-life situation. That's the real question now."

THE TRIALS OF PATARROYO'S VACCINE

Year Begun	Place	End Points	Number and Type of Subjects*	Results	Year Published, Journal
1985	Bogotá, Colombia	Safety, immunogenicity	Monkeys	Safe	1990, *Am. J. Trop. Med.*
1986	Bogotá, Colombia	Immunogenicity, efficacy	Monkeys	Immunogenic, partial protection against parasitemia	1987, *Nature*
1987	Bogotá, Colombia	Efficacy	9 soldiers	Partial protection against parasitemia	1988, *Nature*
1988	Tumaco, Colombia	Efficacy	399 soldiers	82% effective**	1992, *Vaccine*
1988	Tumaco, Colombia	Safety, immunogenicity	292 children 1–14 yrs.	Safe, highly immunogenic	1992, *Vaccine*
1989	Tumaco, Colombia	Safety	15,351 volunteers >1 yr.	Safe	1992, *J. Inf. Dis.*
1989	Las Majadas, Venez.	Efficacy	2360 volunteers >11 yrs.	55% effective**	1994, *J. Inf. Dis.*
1990	CDC, Atlanta	Immunogenicity, efficacy	Monkeys	Partly immunogenic, not effective	1990, *Am. J. Trop. Med.*
1990	Cali, Colombia	Immunogenicity, efficacy	Monkeys	Not immunogenic, not protective	1992, *Am. J. Trop. Med.*
1990	La T, Ecuador	Safety, efficacy, immunogenicity	537 volunteers >1 yr.	Safe, immunogenic, 67% effective**	1994, *Vaccine*
1990	La Tola, Colombia	Efficacy	1548 volunteers >1 yr.	39% effective**	1993, *Lancet*
1991	Costa Marques, Brazil	Efficacy	800 volunteers >7 yrs.	Expected 1995	
1992	Rio Rosario, Col.	Efficacy	1257 volunteers >1 yr.	Expected 1995	
1993	Idete, Tanzania	Efficacy	586 children 1–5 yrs.	31% effective**	1994, *Lancet*
1993	Thai-Myanmar border	Efficacy	1250 children 2–16 yrs.	Expected fall 1995	
1993	Vigia del Furte, Col.	Efficacy	994 volunteers >1 yr.	Expected March 1995	
1994	The Gambia	Efficacy	600 children 6–11 mos.	Expected spring 1995	
1995	Tanzania	Efficacy	ca. 100,000 children	In planning	

*Including controls. **Percent reduction in episodes of symptomatic malaria due to *Plasmodium falciparum*.

Clamoring for campaigns

This question is troubling a lot of minds as Patarroyo receives more and more urgent requests for the vaccine. Bolivia, for example, wants 600,000 doses; Zaire, 10 million. Indonesia wants to build a facility to produce SPf66. An oil-drilling firm in Kenya says it will buy 30 million dollars' worth of the vaccine. And the Colombian government has given the first $8 million to start work on a $20 million production plant for SPf66 that should be fully operational in 1997. In the more immediate future, five malaria-infested countries—Tanzania, Mozambique, the Philippines, Bolivia, and Colombia—are reported to have joined in a plan to vaccinate about a million people with SPf66 in what Patarroyo calls "massive field trials," supported by $3.8 million from the Spanish government.

The debate over what to do now splits the participants along roughly geocultural lines: On one side are Patarroyo, the Colombian government, and Latin American and Spanish researchers, who favor using the vaccine and studying it while doing so; lined up on the other side are WHO and many members of the northern scientific and public-health establishments, who say more research is needed before a decision can be made.

Spain's Alonso admits that "31% [protective efficacy] is not a lot, but you have to relate this figure to the severity of the disease. For a disease that causes 300 million clinical episodes a year, [the vaccine] will prevent at least 100 million episodes." Compare this with the polio vaccine, he says, which is about 80% effective but for a disease that causes only about 100,000 cases a year.

Fears that countries might use such arguments to justify immediate mass application of the Colombian vaccine send shivers up the spines of the "study first" camp. "I'm amazed and appalled at the prospect of countries asking for millions of doses without proper planning and thought," says TDR's Reeve. To jump from only two scientifically solid studies into field use would go against modern conventions of drug development, he adds, citing the 154 clinical trials and 4 to 5 years' development research before the recombinant hepatitis B vaccine was put into widespread use in 1987. Reeve also points out that a vaccine that is 31% effective in a well-controlled clinical trial, "where every child is sure to get the full three shots," will probably reach only 50% of the population in a mass campaign, particularly in Africa. This, Reeve says, would bring down SPf66's protective efficacy to about 15%. "Take off, say, another 5% for nonresponders, and you are left with a 10% efficacy rate, which is little more than background noise."

There are many unanswered questions about SPf66's safety that would justify continued study. Marcel Tanner, head of public health and epidemiology at the Swiss Tropical Institute in Basel and a member of the Tanzania trial team, says, "We don't know, for example, if it is safe and effective in children under 6 months or in newborn infants, and that is important, since most children who die from malaria, at least in Africa, do so between birth and 1 year."

Brian Greenwood, director of Britain's Medical Research Council (MRC) labs in the Gambia, points to another potential risk. He wants to extend a trial of SPf66 now under way in children 6 to 11 months old for another 2 or 3 years "to allow us to determine whether the vaccine, by preventing kids getting malaria in infancy, might be increasing their likelihood of getting cerebral malaria later." This is a possibility, he says, as this often fatal form of malaria peaks at 3 to 4 years of age. "Pure speculation," says Alonso.

To answer some of these questions, Tanner, together with Tanzanian and Spanish research groups, is planning a second study in Tanzania, this time involving at least 100,000 children from 6 months of age—if the Gambia trial shows it is safe to do so in such young children. The trial, he says, will also look at the vaccine's possible effect on malaria mortality and its duration of protection.

Aside from the health risks involved in going straight into applying the vaccine, researchers also worry about what effect it will have on the field. WHO's Lambert says that if the vaccine proves ineffective in campaigns, people could refuse participation in future vaccine trials. Financial donors might also be shy of investing in further studies—the Tanzania trial cost $750,000 for less than 300 vaccinated children. There is also the possibility, he says, that governments of malaria-infested countries will put too much faith in the vaccine and prematurely discard traditional anti-malaria tools, such as drugs and bed nets, that can be effective if properly used. Recent studies in the Gambia have shown that insecticide-impregnated bed nets can reduce deaths among children by up to 40%.

Sitting somewhere between the two camps is TDR's Godal. He also thinks more study is needed: "Our position is clear. We want to support a few large-scale trials to see if the vaccine can slash mortality from malaria. Our calculations show that if it cuts mortality even by 30% and if this effect lasts more than 3 years, SPf66 would be a very cost-effective tool against malaria." Such studies, he adds, should be conducted simultaneously to save time and be "in a real-life situation." He has

therefore asked the WHO's Expanded Program on Immunization (EPI) to define what it would require to add SPf66 to the vaccines it already distributes to the world's children.

A new EPI working group will examine the request shortly, but Mark Kane, EPI medical officer and chair of the group, says SPf66 "doesn't sound like it's ready" for incorporation in the standard EPI package. "We've already got difficulties getting hepatitis B vaccine into routine use, and that's got a 90% protective efficacy."

While this debate is being played out, Patarroyo is beavering away in his Bogotá lab, working on a second-generation SPf66 that has built-in protein fragments designed to block entry of the parasite into red blood cells. He is keeping details of the new vaccine close to his chest, but Colombian sources close to Patarroyo hint that early animal studies are "extremely promising." Could this new vaccine pull the rug from under all the fuss over the current version? "Who knows," says Godal. "It's a bit like buying a computer: You have to plunge in and take what is available now. The only difference is, you know for sure your computer will be obsolete a week after you've bought it. With a malaria vaccine, we've probably got more time to make use of it."

–John Maurice

John Maurice is a science writer in Challex, France.

U.S.–RUSSIAN SPACE SCIENCE

Joint Mission Gets Off to Slow Start

When physician Norm Thagard becomes the first U.S. astronaut to go into orbit aboard a Russian spacecraft on 14 March, his flight will mark more than a symbolic end to a space race begun almost 40 years ago. It will also signal the start of an ambitious cooperative research effort between the United States and Russia to probe the long-term effects of microgravity on the human body.

Despite 20 years of collecting data, researchers have learned surprisingly little about the topic, scientists on both sides agree. U.S. researchers are limited by a space shuttle that can stay in orbit only for about 2 weeks. And the Soviet/Russian program, although it can keep crews aloft for more than a year in its Mir space station, has suffered from inadequate equipment and piecemeal data collection, Western scientists say.

Thagard's flight will begin a seven-mission, 3-year research program aimed at answering such questions as whether astronauts face an increased risk of developing kidney stones on long trips. The joint program is the result of a 1993 agreement between U.S. Vice President Al Gore and Russian Prime Minister Viktor Chernomyrdin, which left National Aeronautics and Space Administration managers scrambling to find a way to translate political promises into scientific reality. NASA, however, is following in the wake of the European Space Agency: A European astronaut conducted life sciences research aboard Mir last October, and two more missions are planned.

The U.S.–Russian effort has gotten off to a rocky start. Much of the U.S. biomedical equipment initially planned for Thagard's use will not reach Mir until well into his 3-month tour. The bulk of the instruments are now being loaded, several months behind schedule, into the Spektr module at a Moscow factory. The large module, a pressurized lab that will be attached to Mir, is not slated for launch until 10 May and will have to be readied for use once in orbit.

Both countries share blame for the delays. "The Americans goofed," says one official involved in the project. "They missed deadlines." Arnauld Nicogossian, NASA's deputy associate administrator for life and microgravity sciences and applications, admits "some things were late." But there have also been problems on the Russian side. Customs officials temporarily detained some U.S. equipment because the proper fees had not been paid. Modifications to the Spektr module also took longer than expected, Nicogossian says.

Despite those glitches, Nicogossian insists the Spektr delay should not hamper Thagard's mission. The astronaut, who will be ferried to Mir aboard a Soyuz spacecraft, will make use of U.S., European, and Russian equipment already aboard Mir, and a Progress supply ship will bring more instruments shortly after Thagard's arrival; a second will follow in April. His activities will include a battery of tests on himself and his fellow travelers accompanying him to Mir to measure the loss of calcium, the reduced production of red blood cells, and the failure of some drugs to become active. This information is critical for planning future missions to Mars, say NASA scientists, and could also provide clues to the way the body works on Earth.

PHOTOS BY NASA

Peace dividend. U.S. astronaut Norman Thagard will be aboard Russia's Mir when it docks in June with Atlantis.

The most complicated part of the joint effort will be the Mir/shuttle missions, the first of which will come at the end of Thagard's sojourn. Early next month, the shuttle Discovery will rendezvous with Mir in a trial run for a docking on 8 June between the Atlantis and the Russian station. Atlantis will bring the pressurized laboratory Spacelab, which contains instruments to examine the human immune system, in particular the production of white blood cells. The U.S. and Russian crews will conduct a joint life sciences research program for the few days the two spacecraft are joined before the shuttle returns to Earth with Thagard and two cosmonauts.

The crews will also examine the microbial and radiation environment on Mir in preparation for the international space station. Russia is now a partner in that venture, which includes Europe, Japan, and Canada. Once the station is under construction in the late 1990s, Russia intends to abandon Mir, and life sciences work will continue on the new, $30 billion facility.

In the meantime, the Mir shuttle program has stretched NASA's already tight budget. The U.S. portion of the program will cost about $100 million, not including the cost of shuttle flights and other extras. The Russian contribution is mostly nonmonetary, consisting of Mir and some supply flights.

The rush to prepare for Thagard's mission did not allow for an open solicitation of experiments, and peer review of existing proposals was done "somewhat after the fact," says Tom Sullivan, the NASA mission scientist. The next flight, however, has attracted widespread interest from laboratories and universities around the country. NASA received about 150 proposals, and the 40 or so winners are expected to be announced next month. With the promise of increased activity in orbit, say Sullivan and other researchers, the once-quiet world of space life sciences has started humming.

–Andrew Lawler