Zeroing in on Brain Toxins

Almost everyone is now sensitized to the possibility that some manmade substances in the environment, such as pesticides, may have a role in causing cancer. But cancer isn't the only possible risk of these compounds, according to a report released last week by the National Research Council (NRC). The report, "Environmental Neurotoxicity," zeroes in on a new, little understood threat: the possibility that some environmental substances contribute to degenerative neurological diseases such as Parkinson's disease, Alzheimer's disease, and amyotrophic lateral sclerosis (Lou Gehrig's disease). The report calls for far more extensive testing of pesticides and other chemicals to determine their potential for toxic effects on the human nervous system—a call that's being resisted by industry but may be heeded in Congress.

The NRC report builds on research over the past decade suggesting that unspecified environmental toxins may play a role in degenerative brain diseases. "It seems plausible that some fraction of chronic neurodegenerative diseases may reflect the long-term consequence of those exposures, just as some fraction of cancer reflects the long-term consequence of chemical exposure," says epidemiologist Philip Landrigan of the Mt. Sinai School of Medicine, who chaired the NRC panel. Perhaps the most dramatic case was an epidemic of a Parkinson's-like illness a decade ago in California among users of a synthetic heroin. Later research showed that a toxic metabolite of the drug was attacking the same brain structures that are affected in Parkinson's disease, raising suspicions that ordinary cases of the disease might also be due to an environmental toxin.

In spite of such suggestive findings, few of the roughly 70,000 chemicals in commercial use have been tested for neurotoxicity, according to the NRC report. Currently, the only products the Environmental Protection Agency (EPA) requires industry to test for neurotoxicity are those the agency designates "high volume"—meaning they're produced in quantities of more than 100,000 kilograms per year or are so widespread that many workers or consumers are likely to come in contact with them, says Suzanne McMaster, an EPA neurotoxicologist. That category includes fewer than 20% of the chemicals EPA licenses. For "low-volume" chemicals, the EPA tries to estimate neurotoxicity by the structure-activity relationship (SAR) method, which is based on a comparison of a chemical's structure to that of a known neurotoxin or nervous-system receptor molecule.

That's not good enough, says the report, which calls the SAR method a "poor basis for predicting neurotoxic potential." The report's rejection of the SAR method is news, according to NRC committee member W. Kent Anger, a behavioral neurotoxicologist at the Oregon Health Sciences University in Portland: "I don't think an authoritative source has said that before." Instead of relying on SARs, the report suggests that the EPA should routinely put chemicals through a three-tiered neurotoxicological testing battery consisting of an initial screen, dose-response studies, and mechanism studies. "With the tiered-testing battery we laid out, there's a reasonable hope of catching most neurotoxins," says Landrigan.

Spokespeople for industry, however, don't think an elaborate new testing scheme is needed for all chemicals. "There's a huge world of chemicals, some of which deserve rigorous testing, others that don't," says Roger O. McClellan, president of the Chemical Industry Institute of Toxicology. Extensive neurotoxicity testing, he says, might be impractically expensive for substances not likely to find a large market. He suggests that the EPA and industry look for a middle ground between SARs and extensive testing.

But some members of Congress think additional surveillance of environmental neurotoxicity would be a good thing. Sponsors of a bill called the "Safety of Pesticides in Food Act," which would require tougher scrutiny of pesticides for neurotoxicity, carcinogenic effects, and reproductive toxicity, are hailing the report. Senator Edward M. Kennedy (D–MA), sponsor of the Senate version, said in a statement last week: "This report makes clear how little we know about the health consequences of the thousands of toxic chemicals that permeate our high-tech society. The most ominous finding is that current risk assessment methods are not sensitive enough to detect real and avoidable risks lurking in our environment." Kennedy and the bill's other supporters think the NRC report may be just the ammunition they need to win the support of reluctant colleagues. ■ RICHARD STONE

Malaria Vaccine on Trial at Last?

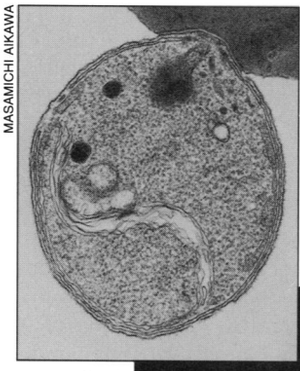
Army medical researchers are planning to seek permission in the next month to test a controversial malaria vaccine in U.S. volunteers. The vaccine was devised in the mid-1980s by Manuel Patarroyo, director of the Institute of Immunology at the Hospital of San Juan de Dios in Bogota, Colombia, and has since received much attention in the media—not all of it flattering. If the Food and Drug Administration (FDA) clears the project, and if a series of two ethical and one scientific review boards gives the nod, Jerry Sadoff, W. Ripley Ballou, and Daniel Gordon at the Walter Reed Army Institute of Research in Washington, D.C. hope to begin recruiting Army personnel for clinical trials as soon as this spring.

The vaccine has made its way to center stage in part because any medication that holds out the hope of reducing the number of new cases of malaria each year (currently around 270 million) deserves attention. Patarroyo himself has fanned this hope by injecting more than 20,000 volunteer patients in Brazil, Columbia, and Venezuela and arguing that the vaccine is protecting 70% or more, an extraordinarily good result. But the Patarroyo vaccine has also been making the news because of the controversy those claims have generated. Many scientists in North America and Europe remain unpersuaded of the vaccine's efficacy. Among the skeptics is Britain's Medical Research Council (MRC), which—as *The New Scientist* has reported—has twice turned down a request by researcher Brian Greenwood to mount field tests in The Gambia, in western Africa. The reason for the refusal: The MRC has concluded that the available data on Patarroyo's vaccine are not adequate to justify the council's support for an experiment in humans.

Indeed, other scientists, including a group at the U.S. Centers for Disease Control (CDC), have had difficulty replicating the animal experiments that preceded human trials of Patarroyo's vaccine. Carlos Campbell, chief of CDC's malaria research lab, says that while there is "enormous interest" in the Patarroyo vaccine, the "details are still not clear." Two vaccine tests with animals have proved "stone cold negative," says Campbell—"ours [at CDC] and one by Socrates Herrera," a colleague of Patarroyo's in Colombia. Patarroyo's human results, meanwhile, are meeting with skepticism because he has not published results of any experiment in which treated volunteers are compared with "controls" receiving a placebo, nor have any of the published experiments used "double-blind" methods to mask the identity of the treated patients.

Although no other researcher has achieved anything like the results Patarroyo has reported, his peers regard him as an extremely competent biochemist. (*Nature* has published two of his accounts of successes in 1987 and 1988 with an early formulation of the vaccine—one in monkeys and the other in military volunteers.) As a result, the Walter Reed group is taking seriously Patarroyo's explanation for other groups' failures to replicate his results: namely, that others have not followed the same procedures he used for formulating the vaccine (*Science*, 27 April 1990, p. 422).

To avoid that problem, the vaccine to be tested at Walter Reed, according to Ripley Ballou, is designed to meet Patarroyo's specifications precisely, and—unlike all earlier batches—it has been produced in an FDA-certified lab that meets standards known as "good manufacturing practices." This makes it possible for scientists to conduct clinical trials in the United States, and also ensures that the vaccine is well characterized and easy to compare to the material used by Patarroyo. Patarroyo himself has collaborated closely with the Walter Reed group in planning the experiment, and one of the chemists involved in making vaccine for him has worked with the company retained to produce the vaccine for Walter Reed, Multiple Peptide Systems of San Diego, California.



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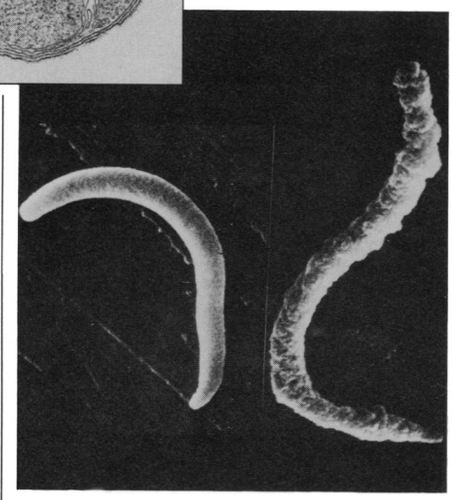

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Cocktail. *Patarroyo's vaccine is a combination of synthetic peptides mimicking surface proteins from both the merozoite* (inset) *and sporozoite stages of the malaria parasite.*

The test material consists of a polymer of four synthetic peptides, each replicating a protein from the most virulent strain of the malaria parasite, *Plasmodium falciparum*. Three of the peptides (only one of which has been fully identified) come from the surface of the asexual blood stage of the parasite called the merozoite, and the fourth comes from the well-studied invasive stage known as the sporozoite.

The Walter Reed group is in the process of finishing all the preclinical animal tests, and the vaccine has been "made and bottled." The scientific team is awaiting final animal potency data before it submits its papers to the FDA and asks the Army surgeon general for clearance to recruit volunteers. Then the clinical work will begin, possibly leading to field trials in which people living in malaria-infested areas are injected with the test material.

Despite the refusal of British authorities to endorse a field trial of this sort, says Stephen Hoffman, chief Navy malaria researcher, a research steering committee on which he sits feels it would be best to take the plunge and investigate the compound on human volunteers. "Given the enormity of the problem," Hoffman says, "it seemed inappropriate to ignore any proposed solution." ■ ELIOT MARSHALL

Tuberculosis Rebounds While Funding Lags

Within the past year, medical microbiologists have had to confront the rebirth of an ancient enemy. Tuberculosis, once thought to be under control in developed countries thanks to an arsenal of effective therapeutic drugs, has risen with a vengeance from the ashes of defeat. The reason: the emergence of new strains of the TB-causing pathogen, *Mycobacterium tuberculosis*, that are resistant to most of the drugs used to treat the disease (see *Science*, 10 January, p. 148). Indeed, the 1990s is shaping up to be the decade of TB, much as the 1980s was the decade of AIDS. Earlier this month, the emerging TB threat came center stage when a handful of leading researchers in the field got together in Bethesda, Maryland, for a workshop convened by Anthony Fauci, director of the National Institute of Allergy and Infectious Diseases (NIAID), to set priorities for federal funding of tuberculosis research.

But while the workshop participants had little trouble agreeing on those priorities, for the moment the available funds look pretty slim. Almost all funding for TB research comes from NIAID, and in 1992 the institute is expected to provide $5.2 million, with the amount slated to rise only to $5.4 million in 1993—barely enough to keep up with inflation—and a drop in the bucket by NIH standards. (By comparison, the institute budgeted $449 million for AIDS research in 1992.) "I don't want to bite the hand that feeds me, but you could say that TB [research] has been underfunded," says Michael D. Iseman, chief of the clinical mycobacteriology service at the National Jewish Center for Immunology and Respiratory Medicine in Denver. "The funding is terrible," agrees Joseph H. Bates, chief of medicine at the University of Arkansas Medical Center, "although everyone is hopeful that things will get better."

In defending NIAID's TB research budget, Fauci says that institute officials didn't become aware of the emerging TB threat until after they'd hashed out the 1993 budget more than a year ago. The level of funding, Fauci told *Science*, "does not reflect the seriousness of our concern." Fauci says he plans to share NIAID's newfound concern with Congress, which can either appropriate more money for TB research or ask NIAID to shift money from other projects—most of which, according to Fauci, are already quite lean.

Should the funds become available, however, the researchers won't have any problem spending them. "There's an awful lot of consensus on what science we need to know," says Barry R. Bloom, a Howard Hughes investigator at the Albert Einstein College of Medicine. Facets of TB research cited as "major objectives" at the workshop include an improved understanding of the bacillus and of TB epidemiology; faster diagnostic tests, especially for the drug-resistant strains; vaccine development and improved TB therapies; and, perhaps most critical, a sharp increase in the number of TB researchers.

"There are no good molecular biologists left in the area," microbiologist Patrick J. Brennan of Colorado State University lamented at the workshop, adding that "all the good biochemistry on the mycobacterium stopped 20 years ago." And basic researchers aren't the only endangered species in tuberculosis research. "The clinical investigator has just about disappeared," says Bates. What will it take to lure talented researchers back into the field? "If you provide dollars to do research," says Bates, "they'll come." And that, for the moment, is the problem—dollars. ■ RICHARD STONE