Agent Orange's Bitter Harvest

New findings paint a more sinister picture of the Vietnam War herbicide; scientists are trying to revive an epic study of its effects on U.S. veterans and clarify its legacy in Vietnam

HANOI—Several children and young adults sit at a table, fiddling with plastic blocks and colored rings with the self-absorption of toddlers. "We teach them small skills. How to wash hands. How to play with toys, distinguish colors," explains Nguyen Thi Oanh, a teacher at Friendship Village, a rehabilitation center in Van Canh, west of Hanoi. The students, 9 to 24 years old but with limited mental development, will spend a few years here and then return to their home villages. During rehab, Oanh says, "some kids get a little bit better." Others do not.

This scene may resonate among health workers around the world who have run similar rehab sessions. But in Vietnam, it resonates with the trauma of war. The 120 children and young adults from 34 provinces at Friendship Village share one thing in common: Their parents or grandparents claim to have been in areas where the U.S. military 4 decades ago used herbicides—the most notorious being Agent Orange—to destroy crops and strip forest canopy to flush out the enemy.

Vietnam claims that the children's disabilities were caused by parental exposures to Agent Orange. Western scientists have long been at odds with their Vietnamese counterparts over the strength of evidence correlating exposure to dioxin—a toxic contaminant of the herbicide—and illnesses in individuals, particularly birth defects. "The Vietnamese government is using malformed babies as a symbol of Agent Orange damage," says Arnold Schecter, a toxicologist at the University of Texas School of Public Health in Dallas, who remains cautious about making associations after studying Agent Orange for more than 20 years.

In Vietnam, there is far less ambiguity. "The number of child victims could be in the 100,000s," says Dang Vu Dung, director of Friendship Village, run on donations from overseas veterans. Countrywide, roughly 3 million people are Agent Orange victims, asserts Nguyen Trong Nhan, vice president of the Vietnam Association for Victims of Agent Orange/Dioxin (VAVA), a nongovernmental organization in Hanoi.

The long-term effects of Agent Orange may never be known, now that an ambitious attempt to analyze them has ended. Late last year, the U.S. Department of Defense pulled the plug on a 20-year-long health study of U.S. veterans involved in Operation Ranch Hand, which sprayed 95% of the Agent

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Sowing trouble. U.S. Air Force planes spray Agent Orange defoliant over Vietnam in 1966.

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Orange and other herbicides used in Vietnam. The $140 million research effort was "the most detailed study of human exposures ever done," says epidemiologist Joel Michalek of the University of Texas Health Science Center in San Antonio, who until 2005 was a principal investigator of the Air Force study. The firmest link it uncovered was between Agent Orange and an elevated risk of diabetes. Otherwise, Michalek says, "there has been little or nothing to say—until now." A cancer signal is just beginning to emerge from the data, he claims, as are subtle physiological changes such as suppressed testosterone levels and prostate growth.

The decision to halt Ranch Hand stunned many researchers. "It will be a tremendous loss to science if it is not continued," says Linda Birnbaum, chief of the U.S. Environmental Protection Agency's (EPA's) experimental toxicology division in Research Triangle Park, North Carolina. A proposal to resurrect it is circulating on Capitol Hill. By law, the Air Force must transfer custody of existing Ranch Hand data and specimens to the U.S. National Academies, which hopes to make them available for further research.

Another day of reckoning is on the horizon—this one for the Vietnamese who claim to have been injured by Agent Orange. This spring, in a U.S. appeals court, oral arguments are expected to begin in a class-action suit brought by Vietnamese citizens against Agent Orange manufacturers. (The claims had been dismissed by a lower court in 2005.) The claimants demand compensation like that given to U.S. veterans who handled Agent Orange and contracted certain illnesses. "It is time for the U.S. government and chemical companies involved in the war to take responsibility for the damage caused by their actions and products," says epidemiologist Tuan Nguyen of the Garvan Institute of Medical Research in Sydney, Australia.

Bitter feelings threaten the blossoming relationship between the United States and Vietnam. "Agent Orange is a very sensitive, very delicate, very political issue—and very controversial," Schecter says. In a small gesture, the U.S. government has pledged to assist Vietnam in cleaning up several hot spots where soil dioxin levels are sky-high.

Researchers from both countries hope this will kindle fresh interest in a joint probe. "We are really ready for cooperation with the United States—as long as it is based on mutual benefits and mutual respect," says toxicologist Le Ke Son, director general of Vietnam's "national steering committee for the overcoming of the consequences of toxic chemicals used by USA in the war in Vietnam," or simply "Committee 33." But U.S. experts have found Committee 33 rigid and opaque and therefore hard to work with. Says Michalek, "Studies in Vietnam are going to be difficult."

True colors

The U.S. and South Vietnamese air forces, mostly using military transport planes, began spraying herbicides in the fall of 1962. Over the next decade, they unloaded some 77 million liters of herbicides on 2.6 million hectares of south and central Vietnam. For the first few years, the main herbicide was Agent Purple, a mix of 2,4-dichlorophenoxyacetic acid (2,4-D) and two forms of 2,4,5-trichlorophenoxyacetic acid (2,4,5-T). Then in 1965, the military deployed Agent Orange, a faster-acting defoliant consisting of 2,4-D and a single form (*n*-butyl ester) of 2,4,5-T. In a painstaking reanalysis of herbicide use during the Vietnam War, Columbia University chemist Jeanne Mager Stellman and her colleagues estimated that over 6 years, 45 million liters of Agent Orange were sprayed (*Nature*, 17 April 2003, p. 681).

Chemical clearance. Normal mangroves (*top*) and a forest 5 years after defoliation.

These agents were laced with a long-lived contaminant, 2,3,7,8-tetrachlorodibenzoparadioxin (TCDD). It's unclear precisely how much dioxin rained down on Vietnam. Stellman's group adopted a "conservative" value of 3 parts per million of TCDD in Agent Orange, although levels "could be fourfold or more higher," they assert. About 10% of Vietnam took a direct hit.

By the late 1960s, Western researchers had evidence that 2,4-D and 2,4,5-T cause birth defects in mice; they were alarmed as well by anecdotal reports of birth defects in Vietnam attributed to the herbicides. In a resolution at its annual meeting in 1969, AAAS (publisher of *Science*) urged the Defense Department to "immediately cease all use of 2,4-D and 2,4,5-T in Vietnam." As criticism of the war intensified, the U.S. military banned the herbicides in April 1970, although Ranch Hand operations didn't cease until late in 1971, and South Vietnamese forces continued to dip into herbicide stockpiles until the war ended in 1975.

But whereas 2,4-D and 2,4,5-T "are not innocuous compounds," Birnbaum notes, evidence soon pointed to a darker villain: dioxin.

A toxic trail

In the past 3 decades, studies have revealed that dioxin causes many harmful effects in animals—birth defects, cancers, and endocrine disorders—sometimes at vanishingly low concentrations. In a rogue's gallery of 75 known forms of dioxin, TCDD is the nastiest. "From fish through primates, it's the most toxic," Birnbaum says, perturbing "lots of different systems in the body." Significantly, it binds to the aryl hydrocarbon receptor, a key regulatory protein. As a result of this unholy coupling, dioxin throws a wrench into processes as diverse as normal homeostasis and aging. (Ukraine's president, Victor Yushchenko, was deliberately poisoned with TCDD in 2004.)

It has, however, been difficult to probe for links between dioxin and human illness. "Thank goodness, very few people in the world are ever exposed to high levels," Birnbaum says. But those with high exposures—in rare occupational accidents and industrial disasters—have suffered chloracne, a severe skin disorder, and transient symptoms of poisoning. Studies have also indicated that dioxin might trigger or abet cancer development and possibly heart disease years after exposure.

Exposures in Vietnam are hard to quantify. Stellman's team estimates that more than 3000 villages with at least 2.1 million people were "sprayed directly" with herbicides, although the number potentially exposed could be as high as 4.8 million. "There are no good records as to who lived in a certain village at a certain time," says Michalek. In more than 30 trips to Vietnam since 1983 to document TCDD in humans, wildlife, food, and

Potent symbol. Children of parents or grandparents exposed to Agent Orange attend a rehabilitation center at Friendship Village near Hanoi; Vietnam blames their problems on Agent Orange.

soil, Schecter and John Constable of Harvard University have found elevated dioxin levels in many of the roughly 4000 people they have tested. Schecter says that a handful of individuals living near a wartime herbicide storage area, Bien Hoa, had TCDD blood levels exceeding 400 parts per trillion. (The U.S. population averages 1 or 2 ppt.)

In the United States, in response to pressure from veterans' groups, the Air Force in the late 1970s began planning a study to track the health of some 1200 Ranch Hand veterans and a control group: veterans not exposed to Agent Orange. The research also examined both cohorts' roughly 8500 children. "We launched the study knowing next to nothing about the exposure profiles"—how much dioxin each vet absorbed, says Michalek, who started on the project in the late 1970s when he was with the Air Force Research Laboratory at Brooks Air Force Base in Texas.

With veterans blaming Agent Orange for an array of ills, the Air Force scientists opted for a broad approach to data collection—and took some heat for that. "The study was seen as seriously flawed," asserts Stellman, who states that it began as "too much of a fishing expedition, measuring everything and anything with too few scientific hypotheses."

In 1987, Ranch Hand researchers began to measure dioxin levels in veterans' blood samples. It was revelatory. "Many people who thought they were highly exposed actually were not," says Birnbaum. "There were very few people with high levels." Michalek and his colleagues sorted veterans into low-, medium-, or high-exposure categories. In 1995, that rough cut at estimating exposure turned up a clear hit: Diabetes risk increased with exposure. Over the next decade, however, other findings were frustratingly indistinct.

Michalek has since reanalyzed the data, zeroing in on veterans who were in Vietnam during or prior to 1968 and were involved in at least 90 days of herbicide spraying. He also excluded vets who spent more than 2 years in Southeast Asia. (Veterans in the control group with such extended deployments are at higher risk of cancer—possibly from exposure to DDT during a World Health Organization campaign in the 1960s to eliminate malaria in the region, Michalek speculates.) The new analysis uncovered "a stronger and clearer trend" of a dose-dependent risk for diabetes and cancer, says Michalek, who intends to submit his findings to a peer-reviewed journal later this month. He expects heavy flak: "Critics will accuse me of slicing and dicing the data," he says.

He and others say it would be a mistake to walk away now. "Certain chronic effects can take years and years to develop," says Birnbaum. And although some experts assailed the study's design, a panel of the National Academies' Institute of Medicine (IOM) concluded last year that "the data appear to be of high quality and the specimens well preserved." The Air Force will transfer Ranch Hand data and specimens to the academies by the end of September. "If we subsequently receive funding to manage the assets and permission from the research subjects, we intend to make the materials available for further analysis," says David Butler, an IOM senior program officer. And IOM next month will convene a panel to advise the Department of Veterans Affairs (VA) on how to apply the Stellman group's exposure model to studies of U.S. veterans. Michalek's university, meanwhile, sent a proposal late last year to several members of Congress and key committees seeking support for a $2-million-per-year Ranch Hand extension.

Congress has intervened before: It passed the Agent Orange Act in 1991, mandating care for veterans known to have been exposed to Agent Orange. The act also called for a definition of illnesses attributable to Agent Orange, as a basis for compensating sick veterans. Toward this end, the VA enlisted IOM to review the health effects of exposure to herbicides used in Vietnam. IOM's landmark report, *Veterans and Agent Orange*, came out in 1994; by law it must be updated every 2 years until 2014. The latest update, published in 2004, concludes that there is "sufficient evidence of an association" between herbicide exposure and five ailments: chronic lymphocytic leukemia, soft-tissue sarcoma, non-Hodgkin's lymphoma, Hodgkin's disease, and chloracne (see table).

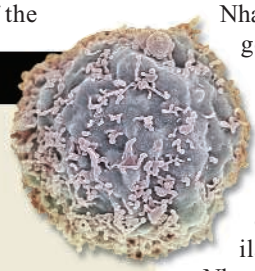
Of all categories of illness blamed on Agent Orange, the most divisive, perhaps, is birth defects. This "remains one of the most contentious issues in science," says Nguyen of the Garvan Institute. According to VAVA's Nhan, the rate of severe congenital malformations in herbicide-exposed Vietnamese populations is 2.95%, compared to 0.74% in nonexposed populations. Grandchildren are afflicted at a similar disproportionate rate, Nhan notes. Government publications about the herbicides are filled with heartrending pictures of deformed children. Reports of families with multiple malformed children abound.

In contrast, the IOM panel has noted "limited or suggestive" evidence linking herbicide exposure and one congenital defect: spina bifida, a malformation of the spinal

Herbicides and Ill Health

SUFFICIENT EVIDENCE OF AN ASSOCIATION
Chronic lymphocytic leukemia (*right*)
Soft-tissue sarcoma
Non-Hodgkin's lymphoma
Hodgkin's disease
Chloracne

LIMITED OR SUGGESTIVE EVIDENCE OF AN ASSOCIATION
Respiratory cancer (lung and bronchus, larynx, and trachea)
Prostate cancer
Multiple myeloma
Early-onset transient peripheral neuropathy
Porphyria cutanea tarda
Type 2 diabetes mellitis
Spina bifida in offspring of exposed individuals



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cord. For all other birth defects, the panel concluded that evidence for an association was "inadequate or insufficient."

This long-running debate has been reignited. A team led by Nguyen for the first time pooled published data with unpublished data from Vietnamese studies of veterans and sprayed civilians. Their meta-analysis of 22 studies, half of which were unpublished, found a "substantially greater" association between Agent Orange exposure and birth defects in Vietnamese populations than in U.S. veterans. Overall, people who believe they were exposed to Agent Orange were almost twice as likely to have a child with birth defects as were unexposed people, Nguyen's group reported last October in the *International Journal of Epidemiology*.

The study has received mixed reviews. "I don't think using unpublished data is a good way to do a meta-analysis," says Schecter, who believes that poor nutrition, infections, and genetic flaws are responsible for most malformations seen in Vietnamese children. Michalek, on the other hand, says Nguyen and colleagues "did the best they could with available data." Nguyen notes that the Vietnamese researchers have had a "hard time" submitting their findings to international journals. "I certainly hope that they will publish their work," he says.

Whether the health effects can be brought into sharper focus is unknown. A few years ago, prospects were looking good. In March 2002, the U.S. and Vietnamese governments signed a research framework to probe Agent Orange effects. "Agreeing to do the research is the easy part," Anne Sassaman, then an official with the U.S. National Institute of Environmental Health Sciences (NIEHS), said at the time. "The more difficult task will be to develop research studies that are definitive and address the underlying causes of disease in Vietnam."

NIEHS thought it had a viable project in sight. In 2003, the agency committed $3.5 million to a study led by David Carpenter of the University at Albany in New York, to probe the possible relation between Agent Orange and birth defects. But talks over a U.S.–Vietnam cooperation agreement foundered. "Without it, the research was impossible to implement," says Committee 33's Son. U.S. officials, including the ambassador to Vietnam and the health attaché, "worked very hard with the Vietnamese but ran into constant roadblocks," says one U.S. scientist. With talks stalemated, NIEHS shelved the Albany study in February 2005.

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Seeking closure

In a common room of a dormitory at Friendship Village, Tran Van Tham, a retired lieutenant in the Vietnam People's Army, and several other veterans are lounging under a portrait of Ho Chi Minh, the leader with the white-streaked Fu Manchu mustache and goatee who orchestrated the North's victory 30 years ago. Whereas disabled children stay for rehabilitation for up to 3 years, veterans cycle through for a month at a time for health checks. "We reminisce, but mostly are here to enjoy life. We feel better, spiritually," says Tham.

Years ago, Tham's two babies succumbed to hydrocephaly and other defects, he says. He blames wartime Agent Orange exposure. Nevertheless, Tham says, eyes glistening, "we can forgive American veterans." But Agent Orange victims are a burden on Vietnam, he says. "We support our government's policy to close the past and look to the future with the United States," adds Nhan. "But we cannot ignore Agent Orange victims." In 2000, Vietnam introduced a program to compensate people who claim disability from Agent Orange exposure. But Nguyen says that each person gets only a few U.S. dollars per month. He estimates that Vietnam needs hundreds of millions of dollars to care for all victims.

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—Tran Van Tham, Vietnam People's Army

In 2004, VAVA, exasperated after years of pleas for U.S. aid went unanswered, filed a class-action suit in U.S. District Court against 37 companies that supplied herbicide chemicals to the U.S. military during the Vietnam War. "We had hoped the United States would respond with goodwill and regarded the lawsuit as a last resort," says Nhan.

The claims were dismissed in March 2005. In a 233-page decision, Senior District Judge Jack B. Weinstein ruled that the companies could not be sued as government contractors. Nor was he persuaded by the scientific case. "No study or technique presented to the court has demonstrated how it is now possible to connect the herbicides supplied by any defendant to exposure by any plaintiff to dioxin from that defendant's herbicide," he wrote. The decision "was a great surprise," says Nhan. The plaintiffs appealed to the 2nd Circuit Court of Appeals in New York City, and oral arguments could be heard as early as April.

The plaintiffs' first challenge is to convince the appeals court that the companies can be sued. If they succeed, they would then have to refute Weinstein's conclusions about the science. "The fact that diseases were experienced by some people after spraying does not suffice to prove general or specific causation," the judge wrote. "Proof of causal connection depends primarily upon substantial epidemiological and other scientific data."

That's a tough argument to overcome, given the paucity of solid epidemiological data. To carry out a high-quality study of human health effects in Vietnam would require "a huge amount of money," says Birnbaum. The "real hurdle," adds Sassaman, who recently retired from NIEHS, "is to get the appropriate scientists and scientific expertise engaged in truly collaborative research." With that in mind, she says, NIEHS has just launched a program to fund junior researchers from Vietnam and other developing countries to work up to 2 years in labs of NIEHS-funded scientists.

Others are taking direct action to eliminate dioxin hot spots in Vietnam. International experts, working with Vietnamese counterparts, have identified nearly 100,000 square meters of heavily contaminated soil in several places where herbicides were stored during the war, says Son. Near Da Nang Airport, he says, TCDD levels in soil reach 35 parts per billion—35 times the permissible level. "Hundreds of thousands of tons" of soil will have to be dug up and stored or treated to remove dioxins, Son says. Last month, the Ford Foundation awarded $460,000 to Hatfield Consultants, an environmental firm in West Vancouver, Canada, to assist at Da Nang.

The U.N. Development Programme, with support from EPA and the Ford Foundation, is setting up a $60 million trust fund for cleanup efforts and to improve the economy of villages near the hot spots. Vietnam's Ministry of Defense has already commenced cleanup at Bien Hoa. "We should get rid of these hot spots," says Birnbaum. "We know that dioxin is bad stuff."

There may be no consensus on exactly how potent dioxin is as a cause of disease and disfigurement. But people do seem to agree that purging the land of the last vestiges of the Vietnam War—particularly the chemical residues of Agent Orange—is something worth fighting for.

–RICHARD STONE