THE AGENT ORANGE MYSTERY

EARTH

By Pamela Weintraub

Bill Singley shivered as he trudged past the ramshackle brownstones of South Broad Street. The hefty martial arts instructor made his way to the first-floor office of number 1427 and fell painfully into a chair. Every muscle depleted, each joint throbbing with Philadelphia's latest chill, he wondered whether he'd ever teach karate again.

The young internist who finally invited Singley into the bare inner office didn't look as if he could offer much hope. He simply fixed his patient with a blunt gaze and solemnly began his exam. After 30 minutes Dr. Ronald Codario could tell Singley only that his liver was bloated and his nervous system damaged.

By June 1981, Dr. Codario had Singley hospitalized for a "workup." A body scan and biopsy told him that the distraught patient's scarred liver had deteriorated like an alcoholic's, though Singley insisted he rarely drank. Then, in the following weeks, Singley's symptoms mounted: His fingers and toes grew numb; his head and abdomen throbbed; he became anxious and confused.

Codario couldn't decipher the cause of the strange illness, but he did know that Singley was a Vietnam veteran. Before long, he started wondering whether the symptoms might not be due to the notorious agent orange—a herbicide that had been dumped on Vietnam to destroy crops that fed and camouflaged enemy troops. Codario told Singley he'd probably been exposed to some kind of toxin and advised him to see a lawyer.

A few weeks later Codario received a call from Hy Mayerson, a Philadelphia attorney who represented vets with illnesses they claimed were caused by agent orange. "Would you like to see some other veterans who've had exposure?" Mayerson asked. "You might be able to help." Codario said sure, and the next day he received weeks of background reading in the mail.

Agent orange, Codario learned, was one of many herbicides sprayed in Vietnam during the 1960s and 1970s. Given its name because it was shipped in orange-striped barrels, agent orange was made largely of a chemical called phenoxyacetic acid. It was usually contaminated with a small molecule known as dioxin, said by some to be the most potent toxin on Earth. Eleven thousand veterans were suing agent orange manufacturers for what they claimed were dioxin's dire side effects: depression, loss of sex drive, joint pain, even cancer. Large numbers of their children, they charged, were being born with deformed hearts, spines, and limbs.

But the experts said there was no real evidence—no *biochemical* evidence—to support such claims. The veterans' troubles, these experts said, were nothing more than a potpourri of unrelated symptoms afflicting the general population in roughly the same proportions.

After examining about 50 or 60 veterans referred by Mayerson, however, Codario observed a strange pattern that made him think otherwise. Like Singley, veteran after veteran complained of personality changes, numbness, aching joints, and extreme sensitivity to sunlight. Amazingly, almost all of them seemed to be describing porphyria (pore-fear-ia), the rare disease that drove King George III mad during the American Revolution.

If Codario could *prove* that his patients had some form of porphyria, he would be the first researcher to establish a biochemical link between agent orange and the veterans' symptoms. With such evidence in hand, he'd be well on his way to helping them get the economic and medical aid they'd been denied for years. With a bit of probing, he might even find a cure.

Classical porphyria, Codario knew, results when the liver churns out massive quantities of chemicals known as porphyrins (pore-fur-ins). Porphyrins produced by healthy livers normally combine with iron and protein to form hemoglobin, the crucial pigment in the red blood cell. But sometimes—because of a genetic deficiency, or because of an unwanted chemical—the liver becomes diseased, manufacturing porphyrins in excess. The extra molecules then travel through the body—to the skin, where they cause huge blisters; to the stomach,

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Medical research may soon vindicate veterans who proclaim the dangers of agent orange.

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where they cause abdominal pain; and to the central nervous system and brain, where they cause numbness, paralysis, and schizophrenia.

Delving into the literature on porphyria, Codario soon found a paper that implied his hunch about agent orange might be correct. The dioxin that contaminated agent orange, the paper suggested, could slip into the nucleus of a living cell and alter genetic material so that the cell produced huge quantities of porphyrin.

By now Codario knew he was hot on the trail of something and began scouring the country for a place that could analyze the veterans' urine for any sign of the disease. Finally he learned of the Watson Laboratory, an internationally acclaimed porphyrin center at Abbott-Northwestern Hospital, in Minneapolis. He placed a call to Zbyslaw J. Petryka, the lab's chief research chemist, and explained his hypothesis. "It's a distinct possibility," Petryka told Codario and volunteered to analyze the veterans' urine himself.

Codario spent the next few weeks collecting urine samples for Petryka. Working late into the night with a group of Philadelphia veterans, he first painted 100 containers pitch-black, since light destroys porphyrins. Then he filled each container with the urine of an ailing patient and got the samples to Petryka by early October.

To test for excess porphyrins in the urine, Petryka used a technique called liquid chromatography: First he poured each urine sample on top of a glass column filled with silica powder, then he waited. Heavier molecules would pass through the powder more quickly than lighter ones; if Petryka knew the weight of a molecule, he could determine its exact identity merely by noting when it reached bottom.

Testing sample after sample, the chemist did indeed find large amounts of relatively heavy porphyrins seeping through the powder. Analysis revealed that these porphyrins were similar to those found in the urine of people abusing alcohol, barbiturates, and antidepressants. When such patients stopped their abuse, their porphyrin level usually returned to normal. But even when the researchers excluded from their study all veterans with drug or alcohol problems, they found that 60 percent of the urine samples had two to five times more of these porphyrins than expected.

The findings suggested that the veterans had a form of porphyria. But to be surer, Petryka ran the urine through a test called the Ehrlich reaction, based on the action of the Ehrlich solution. This clear solution turns purple when exposed to a variety of chemicals, including porphobilinogen, a substance that yields porphyrins.

By this past winter, Petryka had mixed urine samples from 151 veterans in test tubes filled with transparent pools of Ehrlich solution. Ninety percent of the tubes glowed violet in seconds. But try as he might, he could find no sign of any of the chemicals that usually induce the color change. He concluded that the purple coloration was due to an unknown substance. Ninety percent of the Vietnam veterans examined by Codario, it seemed, had urine rife with a mystery molecule.

Petryka then found elevated porphyrins and the mystery molecule in the urine of a nine-year-old girl whose mother and father had both served in Vietnam. Although the girl had never been in Vietnam herself, she suffered excruciating pain just as the veterans did. She woke up screaming at night because her ribs ached, and she walked on her toes because her feet hurt.

Petryka has spent the last six months searching for the unknown molecule in the veterans' urine, but so far he's had little luck. "Until the molecule is isolated," he cautions, "we cannot begin to say just *how* it has affected the veterans." Indeed, although the evidence indicates that agent orange is linked to severe physiological problems, the researchers must do far more work before they can absolutely prove that the veterans have a disease.

But Codario, nevertheless, feels the veterans cannot wait for all the answers. *Any* form of porphyria, he explains, can worsen from year to year.

To head off the symptoms, Codario hopes for FDA approval to test a drug called hematin, which inhibits the enzymes that spur porphyrin production. He also suggests there may be a way of eliminating the original toxin, the dioxin itself. Studies with animals, he notes, indicate that dioxin tends to stay in the body indefinitely, circulating from the liver through the bile fluid and back to the liver again. But if a chemical could bind to dioxin during the cycle, preventing it from reentering the liver, it might pass out of the body and stop provoking porphyrin production once and for all. Just such a drug, Codario adds, was recently used to bind molecules of kepone, a poisonous pesticide that behaves like dioxin: the same drug, or one like it, might be made to fight dioxin as well.

The ultimate answer may be far more complex. Vietnam veterans were exposed to a mixture of 15 herbicides and pesticides with names ranging from agent blue (arsenic) to agent purple to agent pink. The soldiers absorbed each of these with the air they breathed, the water they drank, and the food they ate. The combined effect may forever be inestimable.

But, as Codario says, "Even if we never solve the mystery completely, the important thing is to stop telling the veterans there's nothing wrong with them. One hundred fifty of the two hundred people I've examined have porphyrin problems, numb fingers and hands, and an unknown molecule coursing through their systems. It's time to quit the denials and help."