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Agent Orange and Hematologic Malignancies: The Fog of War Still Hovers

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More than 40 years after the Vietnam War, the fog of Agent Orange hangs thick over veterans and those providing their medical care. Aging veterans suffer from an extensive list of diseases, including several hematologic malignancies, deemed related, or possibly related, to exposure to Agent Orange.

Many cases we see may resonate back to historic events that we don't pay much attention to, in part because it is difficult to dissect the details."

—C. Ola Landgren, MD, PhD

The number of affected veterans will likely increase as new conditions are added to the official list of "presumptive diseases" and as controversies are resolved regarding which veterans were affected (and how the U.S. government should compensate and care for them). Although the science connecting Agent Orange exposure and certain hematologic malignancies is sound, the story of Agent Orange is far from clear-cut. It is covered with a sticky mist of politics, controversy, blame, and denial.

"Many cases we see in our clinics may resonate back to historic events that we don't pay much attention to, in part because it is difficult to dissect the details," said **C. Ola Landgren, MD, PhD**, chief of the myeloma service at Memorial Sloan Kettering Cancer Center in New York, who has extensively studied the link between environmental exposures and multiple myeloma (MM).

To help unravel the story, *ASH Clinical News* spoke with Dr. Landgren and *ASH Clinical News* Associate Editor **David Steensma, MD**, about the science behind Agent Orange, the clinical considerations of exposure, and the task of caring for ill veterans.

Making "The List"

The U.S. military sprayed Agent Orange in military operations from 1962 to 1971. In 1969, it became widely known that the 2,4,5-T component of Agent Orange was inadvertently contaminated with the potent dioxin TCDD. (See **SIDEBAR** below.) In response to a growing body of evidence linking dioxin toxicity to adverse health effects and birth outcomes in returning service members and Vietnamese citizens, the military stopped spraying Agent Orange in January 1971.

In 1991, Congress passed the Agent Orange Act, giving the U.S. Department of Veterans Affairs (VA) the authority to declare certain conditions "presumptive" to exposure to Agent Orange/dioxin and to compensate affected veterans for treatment. Qualifying servicemen and women, their spouses, and their biological children with these conditions are eligible to receive compensation, health care, and vocational training from the VA.

The list of conditions includes ischemic heart disease, type 2 diabetes, and a variety of hematologic and other malignancies (**FIGURE**). The VA also presumes that certain birth defects, namely spina

bifida, in children of Vietnam and Korean War veterans are associated with veterans' qualifying military service. Even decades later, though, the list of covered conditions remains in flux.

To address continuing uncertainty about the long-term health effects of Agent Orange in veterans, the 1991 Agent Orange Act also mandated that the National Academy of Medicine (NAM; formerly known as the Institute of Medicine) perform periodic, comprehensive reviews of scientific and clinical information regarding the health effects of exposure to sprayed herbicides.

Congress stipulated that this review be conducted every two years for 10 years from the date of the first review (1994); the mandate was later extended for an additional 10 years. The tenth and final NAM review was released in March 2016.¹ Consultant scientists from the VA and health experts review each new report (the most recent came in at a hefty 1,115 pages) and make final recommendations to the VA about expanding the list of presumptive diseases. The buck stops with the VA Secretary, who makes the final decision.

In the latest round, the VA missed its expected August 2016 deadline for final recommendations. Now, the job of deciding whether thousands more American Veterans of the Vietnam War will qualify for health care and disability pay rests on President Trump's new VA Secretary, **David Shulkin, MD**, an internist and previous Under Secretary of VA for Health in the Obama administration.

As of press time, Secretary Shulkin had not yet decided which new conditions to include on the presumptive list, but he will be choosing from the following: hypertension, bladder cancer, hypothyroidism, and conditions with Parkinson's-like symptoms.

Although NAM had supported the link between Agent Orange and birth defects in the children of Vietnam War veterans, more recent reviews have backpedaled, stating that there is "inadequate and insufficient" evidence supporting this association. Whether spina bifida will be "de-listed" remains to be seen.

Agent Orange, or Aging and Lifestyle?

The latest NAM report, the 10th report mandated by the Agent Orange Act, may also be the last. It is unclear how new conditions will be added to the VA list in the future and, in September 2015, Congress quietly allowed the expiration of a provision of the Agent Orange Act that governed the way the VA Secretary determines whether new conditions are deemed presumptive.² In the 2016 report, the NAM committee made several suggestions for further studies to be carried out by the VA, including studies of paternal transmission of adverse effects to offspring. They also convened an ad hoc committee in March to further study the issue.

Further complicating the matter of VA coverage are the difficulties in discerning between diseases directly related to Agent Orange exposure and those that are likely to develop as people age. "The list of diseases deemed to be associated with Agent Orange includes conditions like type 2 diabetes and ischemic heart disease, which are overwhelmingly not caused by Agent Orange," said Dr. Steensma, who is also senior physician at the Dana-Farber Cancer Institute, where he is leading a study examining the connection between Agent Orange exposure and MDS in Vietnam War veterans.

"Prostate cancer, which is also fairly new to the list, is almost universal as men age, regardless of whether they served in Vietnam."

Indeed, former VA Secretary **Anthony J. Principi, JD**, who served under President George W. Bush from January 2001 to January 2005, has repeatedly called for the VA to do a “clear re-think” about its mission and how it determines eligibility for compensation.

“It’s time to modernize the VA’s antiquated disability compensation system – to develop a new framework that promotes wellness and compensates those whose quality of life and economic well-being have been sacrificed for our sake,” he wrote in a commentary about “fixing the VA mess” in the *Wall Street Journal*.³ “Today, the country actually compensates a significant number of veterans for the expected and ordinary effects of aging based on presumptions. For example, while we must compensate veterans for diseases linked to exposure to environmental hazards on the battlefield, we should do so only when those decisions are based on sound scientific and medical evidence that the diseases are caused by such exposures.”

He also noted that 80 percent of the more than 1 million new insurance claims filed annually with the VA are filed by veterans whose service time predates September 11, 2001. Thirty-seven percent of those are filed by Vietnam War veterans, which is nearly double the number filed by recently discharged veterans.

Missing Myelodysplastic Syndromes

Veterans seeking VA benefits who fall outside the current VA list of confirmed diseases and exposure locations must make a case for a concrete connection between their conditions and herbicide exposure. This case-by-case process is not always successful, said Dr. Steensma. He estimates that only about half of veterans who go before a judge are awarded disability compensation.

“Obviously, politics and financial considerations affect the definition of a ‘presumptive disease,’” he said, adding that determining which conditions make the list can seem almost arbitrary. For example, some conditions deemed by the NAM authors to have “limited or suggestive evidence” of a link to herbicide exposure are added to the presumptive list (such as ischemic heart disease), whereas others with the same NAM designation (such as hypertension) are not.

One condition that has not made the cut, but that Dr. Steensma would like to see added, is myelodysplastic syndromes (MDS).

“Tens of thousands of veterans who served in the Vietnam conflict were exposed to a toxic mix of chemicals that include known carcinogens that can injure bone marrow cells or cause DNA mutations,” said Dr. Steensma. “We have recently learned that to develop MDS, it takes multiple DNA mutations acquired over time, and so remote exposures may contribute to specific mutations in MDS in this patient population.”

With funding from the Aplastic Anemia and MDS International Foundation, Dr. Steensma launched the Agent Orange MDS-Veterans Study at the Dana-Farber Cancer Institute in November 2016. Researchers are hoping to recruit at least 100 Vietnam War veterans who qualify as presumptively exposed to Agent Orange and will compare their DNA samples with those from a control group of age-matched patients who did not serve in Southeast Asia.

“Many of the veterans who served in Vietnam and are now getting MDS or other diseases of aging are keen to know if their conditions might be linked to Agent Orange and its contaminants,” he said.

“We will never be able to prove causality definitively, but we are looking for a particular genetic signature in the veterans’ samples that we might also see in cases of a particular type of MDS that develops from DNA damage – say, from exposure to radiation or chemotherapy,” Dr. Steensma explained. “We want to see if these veterans have a pattern consistent with MDS that results from DNA damage after exposure to these environmental elements, or if they show a genetic pattern consistent with cases of MDS that come out of the blue, so to speak.”

One frustration for Dr. Steensma is that MDS is often misunderstood. Some may think it is “just an anemia” – including some of the judges who are tasked with determining whether veterans have just cause for disability compensation. And it is also not “non-malignant,” as the most recent NAM report labels it. “MDS has been classified as a malignancy by the World Health Organization for about 20 years,” he noted.

Veterans who develop MDS, “which is probably much more likely to be Agent Orange-related than diabetes, have to go the long way to get benefits,” Dr. Steensma said. If MDS were added to the coverage list, patients would be able to claim 100 percent disability. The potential disability payment could be as high as \$35,000 per year so, understandably, the people who hold the purse strings are hesitant to expand the list. That other conditions for which there is far less evidence are included on the list “just boggles the mind,” he said.

The Politics of Exposure Locations

Like the list of presumptive diseases, a definitive list of exposure locations is also a moving target. There have been confirmed and unconfirmed reports of Agent Orange’s use beyond Malaysia, Vietnam, and Korea, and it was most likely used in several countries for development and agricultural purposes.

The Department of Defense denies Agent Orange was ever used outside Vietnam, military bases in Thailand, and the Korean demilitarized zone – meaning that veterans like Master Sergeant Leroy Foster, who claims to have routinely sprayed Agent Orange to control vegetation around Andersen Air Force Base in Guam during the Vietnam War, and to have multiple diseases as a result of this exposure, is ineligible for VA benefits for his ailments.

On February 1, 2017, Representative Dennis Ross (R-FL) introduced the FOSTER Act, (Fighting for Orange-Stricken Territories in the Eastern Region), a reference to Master Sergeant Foster. The law would provide presumptive Agent Orange exposure status to Vietnam War-era veterans who served in Guam, the Commonwealth of the Northern Mariana Islands, and American Samoa.⁴

Other servicemen have corroborated Master Sergeant Foster’s claims that Agent Orange was used at Andersen, and the government of Guam recently announced that newly appointed Administrator of the U.S. Environmental Protection Agency **Scott Pruitt** has promised to help test for signs of the toxic herbicide residue on and around the island.⁵

The Big Question

The question of whether Agent Orange causes cancer and a multitude of other diseases has been extensively studied for more than 45 years. These studies are not limited to Vietnam veterans; researchers are conducting environmental, occupational, and case-control studies among herbicide-exposed workers in Canada, Denmark, New Zealand, and other countries.

Regarding cancer, the latest NAM report summarizes the evidence to date:

There is sufficient evidence of an association between the chemicals of interest (COIs) and soft tissue sarcomas and B-cell lymphomas (Hodgkin lymphoma [HL], non-Hodgkin lymphomas [NHL], chronic lymphocytic leukemia, hairy cell leukemia).

There is limited or suggestive evidence of an association between the COIs and bladder cancer; laryngeal cancer; cancers of the lung, bronchus, or trachea; prostate cancer; MM; and amyloid light-chain amyloidosis.

There is inadequate or insufficient evidence to determine whether there is an association between the COIs and any other specific type of cancer.

Lymphohematopoietic cancers are among the most common types of cancer associated with environmental and therapeutic agents, so it is not surprising that several hematologic malignancies (including chronic B-cell leukemias, HL and NHL, and MM) feature prominently on the VA's list.

Dr. Landgren has spent more than a decade studying the relationship between MM and its precursor, monoclonal gammopathy of undetermined significance (MGUS) – first at the National Cancer Institute and now at Memorial Sloan Kettering.

Not every case of MGUS transforms into MM, but most individuals with MM had MGUS first, making it a precursor worthy of attention.

“About 30,000 people are diagnosed with MM every year, but a few million people are diagnosed with MGUS every year, which is even more common than breast or prostate cancer,” Dr. Landgren said. “Studying MGUS opens up a huge opportunity to approach an understanding of progression markers, or even try to treat it early on to prevent progression.”

After working on a series of studies in farmers and other workers exposed to pesticides, in which pesticide-exposed workers were found to have a two-fold higher prevalence of MGUS than those who had never been exposed, Dr. Landgren focused his efforts on Vietnam War veterans exposed to Agent Orange.⁶

At the time of his study, MM was already on the VA's list of diseases associated with Agent Orange, “so people diagnosed with MM already had coverage, but the decision was not based on any scientific data,” said Dr. Landgren. “Our study was the first to address the question of whether there is an association between Agent Orange and MGUS on a scientific level. We found that there was.”

The study matched 479 veterans who had served in Operation Ranch Hand with 479 U.S. Air Force personnel who had similar duties in Southeast Asia during the same time period but were not involved in herbicide spraying. All participants had serum TCDD levels measured in 1987, 1992, 1997, and 2002 as part of the Air Force Health Study (AFHS), a longitudinal, prospective, epidemiologic study of more than 2,700 men who were followed for approximately 20 years. AFHS was completed in 2006, but extensive health data linked to several types of longitudinally collected biologic specimens – some 91,000 serum, whole blood, urine, semen, and adipose tissue specimens – remain a valuable research resource.

The crude prevalence rate of MGUS was 7.1 percent in the Ranch Hand veterans, compared with 3.1 percent in the comparison group, translating to a 2.4-fold increased risk of MGUS after multivariate adjustment ($p=0.007$).

Ranch Hand veterans also had significantly higher lipid-adjusted TCDD levels compared with the Air Force group ($p < 0.001$), with nearly half having extremely high TCDD levels (> 10.92 parts per trillion; 47.5% vs. 2.5%; $p < 0.001$). Though the investigators observed a trend of increased risk of MGUS with increasing body burden of TCDD, the trend did not reach statistical significance.

The prevalence of MGUS in which immunoglobulin heavy chain is not expressed (light-chain [LC]-MGUS), considered the premalignant precursor of LC-MM, was 2.3 percent in the Ranch Hand veterans, more than twice the rate of the comparison group (0.8%) – a rate similar to the age-standardized prevalence in men reported in a population screening.

This study falls short of proving causality, Dr. Landgren said, but it would be near impossible for any study to do so. “Short of getting people to drink a glass of Agent Orange and then wait and see if they develop myeloma,” he said, “causality will never be shown.”

It is damning evidence nonetheless, and clinicians should pay attention to factors in a patient’s history that could signal exposure to these toxins.

“If a 75-year-old man comes in with back pain, fatigue, and skeletal pain, an experienced doctor will consider that he could have myeloma; if a 40-year-old man comes in with the same complaints, the doctor will likely assume it’s caused by exercise or something else,” Dr. Landgren explained. “But, if that person was exposed to an environmental toxin, that exposure could potentially be linked to their complaints. Being aware of those links and the risks of exposure to toxins might prevent a delayed diagnosis.”

“It’s amazing that we’re still talking about health risks from the Vietnam War decades on,” added Dr. Steensma. “It’s a long legacy, but it’s exciting that we’re still getting new data because there are still things we need to better understand.” —*By Debra L. Beck*

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FIGURE. Presumptive Diseases Associated With Agent Orange Exposure

Amyloid light-chain amyloidosis

Chronic B-cell leukemias

Chloracne (or similar acneiform disease)

Diabetes mellitus type 2

Hodgkin disease

Ischemic heart disease

Multiple myeloma

Non-Hodgkin lymphoma

Parkinson's disease

Peripheral neuropathy, early onset

*Under VA's rating regulations, must be at least 10 percent disabling within one year of herbicide exposure.

Porphyria cutanea tarda

*Under VA's rating regulations, must be at least 10 percent disabling within one year of exposure to herbicides.

Prostate cancer

Respiratory cancers (including lung cancer)

Soft tissue sarcomas (other than osteosarcoma, chondrosarcoma, Kaposi's sarcoma, or mesothelioma)

Source: U.S. Department of Veterans Affairs, "Veterans' Diseases Associated with Agent Orange." Accessed March 27, 2017, from www.publichealth.va.gov/exposures/agentorange/conditions/index.asp.

[Sidebar](#)

Agent Orange Isn't Orange

Before it became known for its more sinister applications, Agent Orange was a relatively innocuous weed-killer and defoliant (a chemical sprayed or dusted on plants to cause their leaves to fall off). Though its notoriety is tied to the U.S. government's extensive use of it as a weapon during the Vietnam War, Agent Orange is actually a British invention. Both the U.S. and British militaries considered the idea of using herbicides to destroy enemy crops during the later stages of World War II, but never pulled the trigger. Just a few years later, though, the British opted to use eco-warfare to gain the upper hand in an unruly colony.

Starting in 1953, the British military commenced aerial spraying of trioxone (a compound that was virtually identical to Agent Orange) to destroy crops and flush guerillas out of the jungle during a communist insurgency in Malaya, then a British colony.

Allegations in the press that this amounted to “chemical warfare” were dismissed by the British government, which claimed that trioxone and similar herbicides had been tested and were considered “harmless to human and animal life.”¹

The U.S. military’s aerial herbicide spray mission in Vietnam was called Operation Ranch Hand; the military personnel who conducted it are referred to as the Ranch Hand veterans. According to a report from the National Academy of Sciences, approximately 20 million gallons of Agent Orange were sprayed in Vietnam during the operation, which ran from 1962 to 1971.² The defoliants were used to clear plants that provided cover to hostile forces and to disrupt agricultural production in enemy areas.

The herbicides used in Vietnam were identified by the color of the band on the 55-gallon drums they were shipped in: Agent Pink, Agent Green, Agent Purple, Agent White, Agent Blue, and Agent Orange. Each agent used slightly different herbicide formulations to achieve maximum defoliant efficacy and clear strategic plots of land. Agent Orange refers specifically to a 50:50 formulation of 2,4-dichlorophenoxyacetic acid (2,4,-D) and 2,4,5-trichlorophenoxyacetic acid (2,4,5-T), but the term is used generically to refer to all of the herbicides sprayed by the U.S. military in Vietnam.

TCDD, or 2,3,7,8-tetrachlorodibenzo-p-dioxin, or just “dioxin,” is formed during the production of 2,4,5-T and is classified as a carcinogen by the International Agency for Research on Cancer. It is also considered possibly teratogenic, although the scientific data supporting a link between Agent Orange/dioxin exposure and birth defects are controversial.

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