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Agent Orange, United States Military Veterans, And Myelodysplastic Syndromes

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Whenever we experience a strange and unexpected event, especially a personal calamity, we naturally want to know: *What caused it? Could it have been prevented?*

For thousands of men and women who served in the Armed Forces of the United States during the Vietnam War era, questions about causation of serious illness, especially when the diagnosis is an unusual condition such as a myelodysplastic syndrome (MDS), can stir up an old ghost: the misty specter of Agent Orange.

I often see Vietnam-era military veterans in my clinic who have been diagnosed with MDS, and they always ask me, “Could Agent Orange exposure have contributed to my bone marrow problem?”

Whether there is a connection between Agent Orange exposure and subsequent development of MDS, and whether veterans who develop MDS are entitled to compensation under the Agent Orange Act, has been an area of some controversy in recent years.

Below, I review some of the facts about Agent Orange and its potential link to MDS, and then discuss some of the complicated politics.

What Is Agent Orange?

Agent Orange is an herbicide that was sprayed in large volumes on the jungles of Southeast Asia during “Operation Ranch Hand” in the Vietnam War between 1962 and 1971. It was used to kill plants that might provide cover to enemy combatants and to disrupt agricultural production (e.g., destroy rice paddies) in hostile areas.

Agent Orange was also sprayed in the Korean Demilitarized Zone in the late 1960s, and it may have been used in other locations, too, such as in tests on U.S. domestic military bases or to control unwanted growth in National Forests. However, details about domestic use have been harder to confirm.

Agent Orange is not orange like Fanta soda pop; instead, it was named that because of the color of the barrels it was shipped in to Asia, more than four decades ago.

There were other “Rainbow herbicides” sprayed in Vietnam, such as Agent Blue and Agent White, but Agent Orange was the most widely used, and is the agent most clearly linked to health risks.

Agent Orange Is Toxic

Agent Orange was meant to be a 50:50 mixture of two herbicides with lengthy chemical names, 2,4,5-trichlorophenoxyacetic acid and 2,4-dichlorophenoxyacetic acid (the latter is still widely used globally as a weed killer).

Unfortunately, the final product was contaminated with a synthetic byproduct, 2,3,7,8-tetrachlorodibenzo-dioxin – TCDD, commonly called “dioxin” – created during the manufacturing process by Dow Chemical and Monsanto. TCDD is a known carcinogen and is recognized as harmful by the World Health Organization’s International Agency on Cancer, the U.S. Environmental Protection Agency, and other global health agencies.

Military veterans have also testified that in the field, Agent Orange was frequently mixed with other unhealthy substances such as kerosene, JP-4 jet fuel, and other toxic aromatic hydrocarbons (i.e., molecules with a benzene ring), in order to facilitate spraying from aircraft.

The Red Cross of Vietnam has claimed that more than 400,000 Vietnamese citizens were killed and a half-million children born with birth defects because of Agent Orange and TCDD exposure in the 1960s. A number of these victims filed an unsuccessful lawsuit against Dow and Monsanto and dozens of other smaller companies in 2004.

While there is a clear connection between exposure to aromatic hydrocarbons and marrow failure – a risk of aplastic anemia and leukemia in workers with occupational exposure to benzene was recognized before 1920 – just how TCDD contributes to subsequent development of cancer or other diseases is less clear, which has caused lingering questions about epidemiologic association. The minimal, “safe” dose of exposure to such agents is unknown. The amount of toxin exposure that results in marrow disease or cancer is likewise not known, but based on other exposures, is clearly different for individual patients, varying in part based on the levels and function of detoxifying enzymes and DNA repair proteins in the patients’ cells.

Agent Orange Has Been Linked To A Number Of Diseases

Throughout the 1970s and 1980s, there was growing concern about illnesses in U.S. service personnel as a result of being exposed to Agent Orange. Therefore, in 1991, as part of the Agent Orange Act legislation, the U.S. Congress asked the Institute of Medicine (IOM) to review the health effects of Agent Orange and its TCDD contaminant, as well as other herbicides used for military purposes.

The IOM is an authoritative non-governmental national academy that includes more than 1,000 distinguished physicians and scientists, who are appointed to advise Congress on policies related to health and medicine. Various IOM committees and task forces have been formed to address specific health issues.

The IOM published its first report on Agent Orange in 1994, summarizing a large body of epidemiologic studies that collectively found that certain diseases were occurring more commonly in veterans exposed to Agent Orange than in unexposed matched control populations.

Does Agent Orange Cause MDS?

There is considerable circumstantial evidence.

In multiple case-control studies, individuals who work in agricultural and petrochemical industries have been found to have a higher incidence of MDS than those who work at other occupations.

The fact that an exposure is remote in time doesn't mean it can't contribute to MDS. A major epidemiological study published in 2011 demonstrated that among Japanese individuals exposed to the Nagasaki and Hiroshima atomic events in 1945, MDS and acute myeloid leukemia continued to be diagnosed at an increased rate when compared to unexposed people of the same age, even 50 years later.

If Agent Orange and hydrocarbon exposure contributes to MDS development years later, what might the mechanism be? Radiation exposure after an atomic bomb explosion, like certain types of chemotherapy or toxic chemical exposure (aromatic hydrocarbons again), causes cells in the body to undergo DNA damage, increasing risk of subsequent cancer development if the damage is not fully repaired by the cells. If the damage occurs in the wrong set of genes, a disease like MDS results.

Recent whole-genome sequencing experiments have confirmed that MDS, like other neoplasms (cancers), require multiple genetic events to occur over a series of time before the full-blown condition develops. If the first of these required events happened as a result of a chemical injury in the 1960s or 1970s, that DNA injury in a bone marrow cell could have made it more likely that MDS would develop later on as a result of subsequent events.

Of course, in an individual case, it can never be said with absolute certainty that a particular exposure "caused" a cancer – just as it cannot be said with certainty that the individual cigarette smoker who develops lung cancer did so specifically because of their smoking history. We all know George Burns-types who smoke heavily yet live to age 100, as well as people who get lung cancer at age 30 without ever smoking at all. Life is unfair that way. So epidemiologists talk about risk factors.

When a disease is common, it can be more difficult to demonstrate that there is a true increase of the disease in people exposed to a risk factor compared to unexposed people.

Men and women who were 22 years old in 1968 (the average age of military combatants in the year of peak U.S. deployment in Southeast Asia) are 66 in 2012, and getting into the peak years of MDS risk (epidemiologic studies in the U.S. indicate that the median age at which MDS is diagnosed is about 71 or 72 years old). So, a lot of people who served in Vietnam are now at the ages where they might have gotten the disease anyway. But given what we know about MDS biology, it seems much more likely that Agent Orange and accompanying toxic hydrocarbon exposure contribute to MDS than to, say, ischemic heart disease or prostate cancer.

Disability Benefits For U.S. Veterans

As a result of the IOM's report, the U.S. Veterans Administration (VA) agreed to provide disability compensation (i.e., a monthly monetary allowance) for veterans who develop one of the diseases linked to Agent Orange. Notably, veterans do not have to prove that they actually had Agent Orange sprayed on them to have their illness deemed "service-connected" and be eligible for compensation, only that they served in Vietnam sometime between January 1962 and May 1975.

Every two years, the IOM updates its list of Agent Orange-associated diseases, which the VA calls "presumptive diseases." The current list can be found on the Veterans Administration website.

It is notable that numerous hematologic malignancies – chronic B cell leukemias, multiple myeloma, light-chain amyloidosis, Hodgkin disease, and non-Hodgkin lymphoma – and some other cancers are on the "presumptive" list, but not MDS or acute myeloid leukemia.

It is also remarkable that many of the conditions on the "presumptive" list, such as type 2 diabetes mellitus and ischemic heart disease, are extremely common in the general U.S. population and are incontrovertibly linked to other non-Agent Orange risk factors, such as obesity, high cholesterol, family history, or cigarette smoking.

Veterans Administration Politics

Clearly, despite the non-partisan and authoritative nature of the IOM, there is more to the decision about what makes it onto the VA "presumptive" list and what does not than just science and epidemiology.

Finances clearly play a role; given the hundreds of thousands of Vietnam-era veterans with common conditions like ischemic heart disease, billions of dollars are at stake. And whenever that much money is in play, shenanigans will inevitably occur; several Congressional representatives have lobbied for diseases to be included or excluded from the "presumptive" list, as if the science could bend to political will.

Veterans who develop a malady that is not on the VA "presumptive" list can still apply for service connection benefits, but they have to show both that they were exposed to herbicides during military service, and that there is "an actual connection" between their disease and Agent Orange exposure. Defining an "actual connection" is left to case reviewers appointed by the VA, who are rarely specialists in the disease under question.

MDS Is Often Misunderstood

I have read a lot of correspondence related to these applications and appeals for VA benefits, and it is clear that the reviewers are often confused by the causes, biological nature, classification, effects on patients, and severity of MDS. This confusion has contributed to considerable ongoing inconsistency in VA decisions, including the approval or denial of benefits to veterans with very similar or even identical diagnoses and degree of impairment.

Unlike the U.S. Supreme Court, Board of Veterans Appeals (BVA) decisions are not precedent setting and are based on a judge's findings in each individual case. When veterans submit their applications and supporting documentation, the outcomes are a crapshoot.

Furthermore, some veterans have been told by BVA administrators that their MDS is indeed considered to be service connected… but that since MDS is only a form of anemia, they are not "disabled" and therefore not entitled to any compensation.

These judgments reflect a grave misunderstanding of the nature of the disease.

MDS is not just anemia – it is a life-threatening marrow failure state, associated with severe fatigue, among other symptoms, and a risk of death from infection or bleeding. Nor is MDS a benign condition; MDS is a neoplasm (malignancy) in almost all cases, and MDS is classified as a cancer by the World Health Organization and by the U.S. National Cancer Institute.

A history of problematic MDS-related terminology, including "preleukemia" or "refractory anemia" (see my related Beacon column), may be contributing to the judges' confusion about the nature of MDS, but that is not an excuse.

How The MDS Community Has Reacted

A number of veterans whose lives have been affected by MDS have become active advocates for more consistent treatment of veterans by the VA and for better understanding of the disease.

For instance, a veteran named Larry Sauger from Michigan has set up a website to bring together veterans suffering from MDS and to serve as an information clearing house.

Another Vietnam-era veteran, Bob Macfarlane from Florida, went so far as to obtain data on MDS diagnoses from the VA via the Freedom of Information Act, which his calculations indicate is diagnosed at a much higher than expected rate among veterans. Bob has appealed directly to VA Secretary Eric Shinseki with his findings (thus far without results), and also went to Chicago with Larry Sauger in late 2010 to testify before the IOM's "Committee for Review of the Health Effects in Vietnam Veterans of Exposure to Herbicides."

However, despite the efforts of these men and other advocates, when the IOM issued its bi-annual report in September 2011, the Institute decided not to add any more conditions to the current list of presumptive diseases (the IOM report, at 800 pages, makes a fine treatment for insomnia). In this document, MDS merits barely a footnote.

Still, Bob emailed me a few weeks ago that he has been told by a number of widows of ex-soldiers who have died of MDS and related conditions, "My husband did not die in Vietnam– he died because of Vietnam." And so, like an old soldier would, he continues to struggle on with this as his motivator.

John Huber, executive director of the Aplastic Anemia & MDS International Foundation, has begun organizing information sessions specific for veterans at Foundation-sponsored patient and family education events across the U.S., in order to give veterans a forum to learn about and discuss Agent Orange and VA-specific concerns.

John is constantly working with MDS patients and their families, and he has been particularly troubled by the documents from the VA in some veterans' cases suggesting that MDS is simply a form of anemia, akin to iron deficiency or kidney failure-associated anemia, or a "mild" problem.

As he says, “The danger and the severity of MDS are not debated in the clinical medical community, and to call MDS anything less than a group of potentially lethal diseases is an error that belittles the men and women struggling with the disease, or who have died of complications of the disease.”

When the Vietnam War ended in April 1975 with withdrawal of U.S. troops from Saigon, I was four years old. I can remember watching the helicopters on a black and white television in our family den – a real 1970s classic with shag carpet and faux paneling – and hearing my parents (or maybe it was Walter Cronkite) saying something about the “long nightmare” finally being over. That judgment was premature. Nearly 40 years later, the Vietnam conflict’s dark legacy continues, including in the MDS clinic.

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