

Agent Orange and Heart Disease: Is There a Connection?

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Spraying Agent Orange: A photo provided by the U.S. Air Force shows four “Ranch Hand” C-123 aircraft spraying liquid defoliant on a suspected Viet Cong position in South Vietnam, September 1965. The four specially equipped planes covered a 1000-foot-wide swath in each pass over the dense vegetation (AP Photo/U.S. Air Force).

IN AUGUST 2011, a patient asked if I would complete a form that he had received from the Veterans Administration. It was an Agent Orange Fast Track Claim for Ischemic Heart Disease. I completed the form, which requested that I provide evidence that my patient, who had served in Vietnam and described his exposure to Agent Orange, had arteriosclerotic heart disease. That was not difficult, as he had already, at the age of 56, undergone a coronary artery angioplasty and stent. I was not aware of a connection between Agent Orange and coronary heart disease.

I learned in May 2013 that compensation was awarded to my patient. I knew that the Veterans Administration, over several years, had recognized Agent Orange exposure as a possible cause of a variety of conditions, predominantly skin disorders and a number of tumors and leukemia. In its most recent deliberations, the Veterans Administration added Parkinson’s disease and perhaps most importantly, ischemic (atherosclerotic) heart disease. This led me to look into the tangled history of Agent

Orange during the Vietnam conflict between 1962 and 1971.

Sifting through the evidence

The United States sprayed Agent Orange, a herbicide, in a highly concentrated form as a defoliant in Vietnam beginning in 1962. Agent Orange was known to contain the contaminant TCDD or 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (dioxin), which is regarded as a highly toxic chemical agent in animals and man (1).

During the decade between 1980 and 1990, as veterans’ groups were asserting that they were suffering effects of toxicity related to exposure to Agent Orange in Vietnam, there were published reports of toxicity

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related to industrial exposures to dioxin (2, 3). As reported in the December 1989 issue of *Cancer*, a study of the cancer risks among Missouri farmers found elevated levels of lip and bone cancer, as well as nasal cavity/sinus and prostate cancer, non-Hodgkin's lymphoma, and multiple myeloma. Smaller elevations were found for cancers of the rectum, liver, and kidney, malignant melanoma, and leukemia. According to the authors, evidence of the cause for the elevated risks for these illnesses "may be strongest for a role of agricultural chemicals, including herbicides, insecticides and fertilizers" (4).

With the increasing volume of scientific literature giving credence to the belief of many Vietnam veterans that exposure to Agent Orange during their military service was related to several debilitating diseases—particularly, non-Hodgkin's lymphoma, soft-tissue sarcoma (malignant tumors that form in muscle fat or fibrous connective tissue), and porphyria cutanea tarda—Vietnam veterans sought disability compensation from the Veterans Administration. During the decade between 1980 and 1990, there were many congressional investigations and reports concerning the possible risks posed to Vietnam veterans exposed to Agent Orange. The evidence for and against a link between exposure to Agent Orange and resulting diseases was ultimately based on statistical analysis of data, which were acknowledged to be inadequate regarding the extent, intensity, and duration of exposure to Agent Orange. It became clear that Agent Orange exposure was not limited to areas that were sprayed directly but that Agent Orange was carried in flowing streams and rivers.

Because of continuing uncertainty about the long-term health effects of the sprayed herbicides on Vietnam veterans, Congress passed the Agent Orange Act of 1991. The legislation directed the Secretary of Veterans Affairs to request the Institute of Medicine (IOM) to perform a comprehensive evaluation of scientific and medical information regarding the health effects of exposure to Agent Orange and other herbicides used in Vietnam and to report to the Veterans Administration every 2 years.

The *Veterans and Agent Orange: Update 2008* (the eighth report in this series) stated the following conclusion: "The authoring committee found suggestive but limited evidence that exposure to Agent Orange and other herbicides used during the Vietnam War is associated with an increased chance of developing ischemic heart disease and Parkinson's disease for Vietnam veterans" (5).

The report from the IOM in 2010 concluded that ischemic heart disease should move from the category of "inadequate or insufficient evidence of an association" into the category of "limited or suggestive evidence of an association. . . ." The report added, "the distinctions among categories are based on statistical association, not on strict causality" (6). As reported in *The Federal Register* on August 31, 2010, "After consideration of the relative strengths and weaknesses of the evidence regarding the chemicals of interest and isch-

emic heart disease. . . which includes a number of studies that showed a strong dose-response relationship and that had good toxicologic data demonstrating biological plausibility, the committee judged that the evidence was adequately informative to advance this health outcome from the 'inadequate or insufficient' category into the 'limited or suggestive' category. . . . The IOM report's discussion demonstrates that there are medical studies that show a correlation between exposure to herbicides and ischemic heart disease. . . . of the nine most informative studies on this issue, five showed strong statistically significant associations between herbicide exposure and Ischemic Heart Disease. The IOM committee noted that the evidence for an association was further strengthened by findings of a dose-response relationship, meaning that the risk of IHD was found to be highest in populations with the highest levels of herbicide exposure" (7). This recommendation led to the Agent Orange Fast Track Claim for Ischemic Heart Disease.

A growing body of scientific evidence now suggests strongly that the connection between Agent Orange and ischemic heart disease is based on sound scientific information. Although the decision was based on the testimonies of Vietnam veterans and epidemiologists, it appears to have a strong biological foundation in an understanding of cell signaling and genomics.

The science behind the decision

It is a story worth telling. As a nephrologist, I have an interest in chronic renal disease. Although much has been written about the treatment of chronic renal failure by dialysis since the ground-breaking work of Belding Scribner (6), the scientific community has gradually come to the realization that although dialysis treatment effectively ameliorates the symptoms—nausea, vomiting, itching, confusion, and weakness—that define "uremia," the long-term consequence of chronic renal failure, not corrected by dialysis, is ischemic heart disease. Chronic renal failure is a powerful risk factor for ischemic heart disease and appears, from observational studies in patients and studies in experimental animals, to be a result of a small protein-bound aryl amine—indoxyl sulfate—which is not removed effectively by conventional hemodialysis or peritoneal dialysis, as it is too large to pass through a dialysis membrane or the peritoneal membrane (8). Indoxyl sulfate is normally secreted by renal tubular cells equipped with organic anion transporters. With the use of the tools of modern molecular biology and genomics, it appears very likely that indoxyl sulfate—a major uremic solute produced in the body from dietary sources—accumulates when renal tubular secretion is limited and mediates a number of effects on gene expression leading to ischemic heart disease. The key step in this story is the binding of indoxyl sulfate to a molecule within the cell cytoplasm, identified as the "aryl hydrocarbon receptor" or AHR: this reaction activates signaling pathways

within the nucleus of the cell, leading, finally, to atherosclerosis (9).

AHR has been recognized for some time as part of the cell's mechanism for disposing of environmental toxins and—you guessed it—the prototype of environmental toxin that binds to AHR is dioxin, a major component of Agent Orange! Based on studies of disease occurrence, the bulk of the toxicity of dioxin has focused on skin changes, endocrine effects, altered immune responses, and a variety of cancers. With the use of new, powerful tools to study gene expression and cell signaling, evidence that indoxyl sulfate—a uremic toxin that is associated with premature and severe arteriosclerotic heart disease in patients undergoing dialysis—activates the same AHR as dioxin (10) provides strong biological evidence that the development of ischemic heart disease—arteriosclerosis—in Vietnam veterans is attributable to dioxin, a major component in Agent Orange.

Although it is a credit to the astuteness of the scientists and epidemiologists who sifted through the often-conflicting clinical data, it is also reassuring to recognize that the decision of the Veterans Administration appears to have a sound biological basis and in a broader sense, to find an example in which “evidence-based medicine” is confirmed by good science.

Evidence-based medicine has been heralded as a paradigm shift that “de-emphasizes intuition, unsystematic clinical experience and pathophysiologic rationale as grounds for clinical decision making,” discarding a tradition of medicine based on careful clinical observation, often the unsystematic observations of a very few highly gifted physicians (11). It is hard to imagine that any paradigm shift could diminish the value of the intuition and unsystematic observations of physicians, such as Charcot, Freud, or Cushing. Rather, the observations of great clinicians were pursued in the laboratory by clinician-scientists and basic scientists—physiolo-

gists, immunologists, biochemists, pharmacologists, and more recently, geneticists and cell and molecular biologists (12).

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