The Long-Term Respiratory Perils of War

The pathway to chronic lung disease is complex. This is evident in entities such as chronic obstructive pulmonary disease, where latent effects of smoking may not manifest for decades, or asbestos-related disease, with exposure latency periods of 20–50 years. In chronic fibrotic lung diseases like idiopathic pulmonary fibrosis (IPF), the timing between inhaled environmental or occupational exposures and disease onset remains poorly characterized. This is largely due to the complexity and relative rarity of IPF and the relationships between genetic predisposition and exposure that may differ between individuals. We remain in nascent stages of understanding how exposures increase the risk of developing IPF, but there are undoubtedly environmental contributors (1, 2).

IPF is a progressive fibrotic lung disease of complex etiology. The proposed pathobiology assumes a genetic predisposition, paired with epithelial injury, aberrant wound healing, and subsequent fibroproliferation, which, if unchecked, progresses to end-stage pulmonary fibrosis (3). One culprit source of injury is cigarette smoking, with consistently elevated odds of disease and a dose–response relationship (4), and IPF appears most prevalent in older White men (5). The U.S. Veterans Administration system, which provided care and long-term health insurance to 0.9% of the insured general population or 3.0 million veterans in 2020, offers a unique opportunity to study IPF (6). IPF is as common in military veterans as in the general Medicare population, with geographic variability in incidence and prevalence, suggesting that beyond simple demographics, there may be occupational or environmental factors mitigating disease risk (7).

From 1962 to 1971, the U.S. military sprayed herbicides over Vietnam to strip the jungle canopy. The most-used chemical mixture sprayed was Agent Orange, which at the time of use was contaminated with 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD), the most toxic form of dioxin. Although estimates vary, the most recent report from the National Academy of Sciences calculated that 77 million liters were applied in Vietnam (8). The fat-soluble nature of TCDD allows it to readily enter the body by attaching to the aryl hydrocarbon receptor protein; once bound to the aryl hydrocarbon receptor, the protein moves to the nucleus, where it influences gene expression and essentially mediates TCDD's toxicity. Once dioxins enter the body, because of their chemical stability and absorption by fat tissue, they can be stored with an estimated half-life of 7–11 years. TCDD has been classified as a carcinogen by the U.S. Environmental Protection Agency and the International Agency for Research on Cancer. It is associated with risk of soft tissue sarcomas, lymphomas, and chronic lymphocytic leukemia, but to date the evidence has been insufficient to determine association with chronic nonmalignant respiratory disease (8).

In this issue of the *Journal*, Kaul and colleagues (pp. 750–757) used a nationwide cohort of U.S. military veterans to characterize the risk of IPF associated with Agent Orange exposure (9). Of 3.6 million male Vietnam veterans receiving care over a 10-year period, nearly 1 million were presumed exposed to Agent Orange, based on a flag specific for Vietnam "boots on the ground" service. Using an administrative claims–based diagnostic algorithm, more than 71,000 cases of IPF were identified, occurring in 2.2% of exposed versus 1.9% of unexposed individuals. In adjusted models, the odds of IPF in Agent Orange–exposed veterans were 8% higher than in those unexposed (odds ratio, 1.08; 95% confidence interval, 1.06–1.10; $P < 0.001$). The attributable fraction of IPF among veterans exposed to Agent Orange was estimated at 7% (95% confidence interval, 5.3–8.7%; $P < 0.001$). Findings were supported across sensitivity analyses, with numerically higher associations when stricter case definitions were used and in analysis restricted to those having served in the Army, a surrogate for higher likelihood of exposure.

This is the first study to identify an association between Agent Orange, a toxin used in war, and the risk of IPF in exposed veterans. It establishes a premise for identifying exposures that increase the risk of IPF not only in the military but also in other occupational and domestic situations. Importantly, it highlights the value of administrative claims–based data to address environmental epidemiology and the importance of characterizing exposures that occur during conflict, given the potential long-term impacts.

The study has important limitations, acknowledged by the authors. Exposure was presumptive and unable to be confirmed, and an exposure–response relationship was not directly explored. However, the sensitivity analysis restricted to Army veterans supports the possibility of a dose–response effect. Furthermore, increasing evidence of a link between inhalation exposures and IPF in veterans has not been matched by increasing inhalation toxicologic studies examining underlying mechanisms. The long latency of clinical manifestation of inhalation injuries and the persistence of TCDD in fat stores speaks to the need for more mechanistic pulmonary toxicologic studies of Agent Orange. Consistent mechanistic data would lend further credence to the plausibility of the findings, although not required. Robustly conducted environmental and occupational epidemiology studies can provide sufficient evidence of association and even causality—often despite an absence of detailed exposure data and incompletely understood mechanisms. For rare diseases and/or those with remote or nonreproducible exposures, such studies may provide the strongest evidence of association. The current study is likely the most robust that will ever be conducted on this topic.

These findings could not be more timely. At the time of writing, war continues to rage in Ukraine, with other active conflicts in several global regions. An estimated 2 billion people live in conflict-affected areas, vulnerable to health and safety hazards (10). Above and beyond physical and psychological trauma, people in these regions may have exposure to respiratory toxins, with potential devastating long-term impacts. The respiratory perils of war may be vast, yet without recognition (and ideally abatement), they could go unrecognized as causes of disease for decades, as shown here with Agent Orange. From a toxicologic exposure perspective, prospective collection of biological samples should be take place now as correlates of exposure in such

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situations, both from residents and military personnel, to characterize direct and epigenetic consequences of exposure that may impact large populations in both the short and long term (11). Planning ahead to understand how exposures cause disease will be critical, and, ideally, such knowledge would prevent further use of chemicals or agents identified and designated as respiratory toxins.

If mistakes of the past are not heralded as lessons, then they are destined to be repeated. When it comes to global respiratory threats as but one consequence of armed conflict, we have much to learn and many lessons to learn from. As clinicians working to prevent and treat lung disease, it is clear that advocating to prevent long-term respiratory perils of war falls quite clearly in our lane. ■

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Of Registries and Disease Classification: Unmasking the Challenges of Pediatric Pulmonary Hypertension

Despite major advances in diagnostic strategies and drug therapies over the past decades, pulmonary hypertension (PH) continues to cause significant morbidity and mortality in diverse pulmonary, cardiac, hematologic, and other systemic disorders in neonates, infants, and children (1, 2). Evidence-based advances in the care of children with PH have been limited due to many challenges, including the heterogeneity of associated conditions; lack of organized multidisciplinary care centers in the past; small numbers of patients at each center; a paucity of quality endpoints for assessing clinical course and response to therapy; and many other factors (1–3). Importantly, despite strong clinical evidence from multicenter randomized trials supporting the use of several PH-targeted drugs for adults, data supporting the safety and efficacy of these agents remains extremely limited for pediatric PH. Clearly, many similarities between adult and pediatric PH exist; however, critical aspects of PH in children can be

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