

The Long Aftermath of the 1991 Gulf War

Soldiers fortunate enough to return from war in sound body have often encountered further problems (1, 2). Nevertheless, the scale and nature of the problems reported by veterans of what we must now call the first Gulf War came as a surprise. Casualties were fortunately extremely light and the duration of fighting short. Yet with the passage of time, a trickle, then a flood, of veterans on both sides of the Atlantic began reporting health problems.

It soon became clear that we were not dealing with a new disease, with anything that affected mortality (3, 4), or with any easily defined, known disease entity (5, 6). Nor, as it turned out, was a classic psychiatric disorder the answer. The textbook war-related psychiatric disorder, post-traumatic stress disorder, was present, of course, but not in sufficient quantity to account for what was a substantial health effect (7). Instead, we were seeing an increase in symptomatic ill health, as a series of large epidemiologic studies from the United States (8), the United Kingdom (9, 10), Canada, Denmark, and Australia (11) all reported similar findings.

There was no shortage of possible culprits. For example, what was then an indisputable threat from chemical and biological weapons made all prudent commanders insist on the widespread use of medical countermeasures to protect the armed forces. The United Kingdom chose to vaccinate our military against not only the usual infective hazards but also against plague, anthrax, and pertussis, the last chosen deliberately to increase the speed of protection against anthrax. Given that all medical interventions, even preventive measures, have side effects, it is reasonable to ask, as many veterans did, whether these countermeasures could have inadvertently caused side effects. In our epidemiologic studies, we did indeed find a very particular interaction between unexplained symptoms and receipt of anthrax vaccine, receipt of multiple vaccines, and place of vaccination (9, 12). We also found evidence of cellular immune activation in our cohort 10 years after the conflict (13). The significance of this finding is not known. However, these possible culprits alone do not account for all of the observed ill health.

Other medical countermeasures used in varying quantities by the coalition forces included pyridostigmine bromide to counter the threat from chemical weapons and pesticides to reduce the risk for parasitic diseases, a traditional burden on soldiers fighting in hostile environments. However, evidence that these agents have played a substantial role is hard to come by, perhaps because of almost insuperable difficulties in determining who was and who was not exposed and the amount of exposure in different individuals (14, 15).

Medical countermeasures were not the only hazards of Gulf War service. The battlefield is by every definition a dangerous place and is made more so by the use of depleted uranium munitions, which provide even more lethal power to those who use them. In thinking about the balance of risks and benefits in using depleted uranium munitions in weapons

and armor, we should not forget that for service personnel on the battlefield, the most immediate dangers arise from the opposing forces. A tank that returns fire presents an immediate life-threatening hazard, one that is rarely present when soldiers use depleted uranium munitions against the tank. But did these munitions have lingering, long-term health effects? Although the evidence remains disputed (16), depleted uranium alone cannot account for a health effect that is as prevalent in rear echelons as in troops in active combat, in the air and sea as much as on the ground.

It was never very likely that *Mycoplasma* infection accounted for the Gulf War health effect. Future historians of medicine and culture may puzzle over why people thought that it was a plausible explanation for Gulf War-related unexplained illnesses. They may conclude that the origins of this belief had nothing to do with the circumstances of the 1991 Gulf War but more to do with the alleged involvement of *Mycoplasma* species in other contested diagnoses, most particularly the chronic fatigue syndrome. This purported connection has never found much favor outside the United States. Nevertheless, for whatever reason, increasing numbers of U.S. veterans were beginning long-term, potentially hazardous antibiotic treatment to deal with the alleged infection. It would have been easy for professionals to ignore this and simply express skepticism and disapproval. However, to their credit, the U.S. Department of Veterans Affairs and the U.S. Department of Defense chose the more open-minded, and expensive, option. They subjected this theory to the only scientific test that matters, the rigors of the large, well-conducted randomized, controlled trial.

The report of that trial, by Donta and colleagues, appears in this issue (17). We are fortunate that it was large enough and conducted diligently enough to give an unequivocal answer for both its primary and secondary end points. Doxycycline treatment has no effect on the health of symptomatic Gulf War veterans. Furthermore, serologic evidence of *Mycoplasma* infection was unrelated to health. In the future, we cannot recommend long-term treatment with doxycycline or similar compounds for symptomatic veterans.

It would, however, be naive to expect that this negative trial will be the end of the matter. Those who firmly believed in the central role of *Mycoplasma* infection in Gulf War veterans' illnesses before the trial did so in the absence of evidence that the rest of us would find compelling. The trial results will not easily persuade adherents to the infection theory of Gulf War veterans' illnesses to change their minds, and we may soon hear their reasons for rejecting the conclusions of the study. We shouldn't let attempts to discredit the trial results deflect us from Donta and colleagues' main conclusion: We need to look elsewhere for the answer to the Gulf War health problem.

So what is the answer? Regrettably, we do not know.

An equally well-designed and well-conducted study of behavioral interventions for the same problems, also conducted by the Department of Veterans Affairs, was not a complete failure, but neither can we call it a great success (18). The trial compared cognitive behavioral therapy with graded exercise therapy, alone and in combination (19). These interventions were based on models derived from studies of the chronic fatigue syndrome, which may be an imperfect model of Gulf War veterans' illnesses.

Symptomatic Gulf War veterans, at least in the United Kingdom, are not feeling any better (20), and the simple truth is we do not really know why nor what to do about it. It is now time to consider the problems of sick Gulf War veterans in the context of other unexplained or ill-defined syndromes that have arisen in the aftermath of other wars, in other times and other places. Indeed, Gulf War veterans' illnesses overlap not only with previous postconflict syndromes, such as soldier's heart or the effort syndrome, but also other unexplained and controversial diagnoses found in nonmilitary settings, such as the chronic fatigue syndrome, multiple chemical sensitivity, or fibromyalgia (21).

It remains our moral obligation to continue to support and assist disabled veterans of the 1991 Gulf War, even if for many we cannot clearly define the exact nature of their problems. The United States is well placed to do this. The public frequently criticizes the Department of Veterans Affairs, but some of us who are passionately concerned with the health of ex-service personnel look across the Atlantic with some envy. In the United Kingdom, we make no special provision for our service personnel once they leave the military, relying instead on our comprehensive health care provision. While this policy is certainly appropriate for most health problems faced by veterans, it may not be suitable for the difficult, complex, yet clearly service-related enigmas, such as Gulf War veterans' illnesses, that provide us with the greatest clinical and epidemiologic challenges.

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