

## Cellular and humoral immune abnormalities in Gulf War veterans

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**Abstract.** We examined 100 symptomatic Gulf War veterans (patients) and 100 controls for immunologic assays. The veterans and controls were compared for the percentage of T cells (CD3); B cells (CD19); helper:suppressor (CD4:CD8) ratio; natural killer (NK) cell activity; mitogenic response to phytohemagglutinin (PHA) and pokeweed mitogen (PWM); level of immune complexes; myelin basic protein (MBP) and striated and smooth muscle autoantibodies; and antibodies against Epstein-Barr virus, cytomegalovirus, herpes simplex virus type 1 (HSV-1), HSV-2, human herpes Type 6 (HHV-6), and Varicella zoster virus (VZV). The percentage of T cells in patients versus controls was not significantly different, whereas a significantly higher proportion of patients had elevated T cells compared with controls. The percentage of B cells was significantly elevated in the patients versus the controls. The NK cell (NK) activity was significantly decreased in the patients (24.8 +/- 16.5 lytic units) versus the controls (37.3 +/- 26.4 lytic units). The percentage of the patients with lower than normal response to PHA and PWM was significantly different from controls. Immune complexes were significantly increased in the patients (53.1 +/- 18.6, mean +/- SD) versus controls (34.6 +/- 14.3). Autoantibody titers directed against MBP and striated or smooth muscle was significantly greater in patients versus controls. Finally, the patients had significantly greater titers of antibodies to the viruses compared with the controls ( $p < 0.001$ ). These immune alterations were detected 2-8 years after participation in the Gulf War. The immune alterations are consistent with exposure to different environmental factors. We conclude that Gulf War syndrome is a multifaceted illness with immune function alterations that may be induced by various factors and are probably associated with chronic fatigue syndrome.

**Conclusions:** Based upon these observations and earlier reports by others, we believe that GWS is a multifactorial disease caused by exposure to a variety of environmental conditions, e.g. xenobiotics, vaccinations and other stressor related conditions of the Gulf War environment as summarized in Figure 3. We believe that the outlined multiple factors along with genetic susceptibility due to polymorphism of paraoxonase, loss of neuropathy target esterase, glutathione S-transferase and cytochrome P450 enzymes, and others, may affect some individuals, resulting in immune dysregulation (Haley et al, 1999; Loewenstein-Liechtenstein et al. 1995; Shields, 1994; Whatt et al, 2000). These immune functional alterations reported herein may cause viral reactivation and induction of proinflammatory cytokines, resulting in chronic fatigue-fibromyalgia-like and other symptoms of GWS (Partaca, 2001; Ferguson and Cassaday, 2001/2002; Rook and Zumia, 1997; Zhang et al, 1999). The variation in individual susceptibility to environmental stresses and toxicants is a new discipline (Toxicogenomics) initiated at NIEHS, which studies the relationship between genes and environmental stressor (Waters et al., 2003). Perhaps, toxicogenomics will enable us to answer why some soldiers developed GWS and others did not. Finally, it appears that additional studies involving asymptomatic deployed GW vs symptomatic GW veterans would be beneficial in further understanding of the immunologic observations presented herein.

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