*Journal of Chronic Fatigue Syndrome 2004; **12**(1):79-83*

Gulf War Veterans: Evidence for Chromosome Alterations and their Significance

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CHROMOSOME ABERRATION ANALYSIS IN PERIPHERAL LYMPHOCYTES OF GULF WAR AND BALKANS WAR VETERANS. Schröder H, Heimers A, Frentzel-Beyme R, Schott A, Hoffmann W. *Radiation Protection Dosimetry* 2003;103:211-220.

A significant portion of veterans who were deployed to the 1990 Gulf War developed Gulf War Illnesses (GWI), which are mainly characterised by persistent muskuloskeletal pain, fatigue, and cognitive problems (concentration, memory, and attention difficulties), and a large number of other signs and symptoms (1). In addition, Gulf War veterans who developed chronic abdominal pain and diarrhea exhibited visceral hypersensitivity in response to experimental visceral pain stimuli, as seen in patients with irritable bowel syndrome (2). Compared with non-Gulf War veteran controls, Gulf War veterans showed significantly higher rates of both Chronic Fatigue Syndrome (odds ratio = 4.8; 95% confidence interval (CI) 3.9-5.9) and post-traumatic stress disorder (odds ratio = 3.1; 95% CI 2.7-3.4) (3). These epidemiological data, however, were based solely on surveys of 15,000 Gulf War veterans and 15,000 non-Gulf War veteran controls, and were not validated by an extensive examination required for the diagnosis of Chronic Fatigue Syndrome. From a systematic review and meta analysis, the authors concluded that compared to service personnel who had not been deployed to the Persian Gulf Theatre of Operations, Gulf War veterans had an increased risk for both post-traumatic stress disorder (odds ratio = 3.17; 95% CI 2.16-4.65) and common mental disorders (odds ratio = 2.04; 95% CI 1.94-2.15) (4). However, the authors support the view that other factors must be contributing to GWI, in addition to any increase in psychiatric disorders (4). Others are convinced that GWI reflect pathophysiologic and biochemical processes (5,6), a view that is supported by the observed higher prevalence of birth defects (tricuspid valve insufficiency, aortic valve stenosis, renal agenesis, and hypospadias) among infants conceived postwar to Gulf War veterans of both sexes (7). A pathophysiologic nature for GWI might explain why both cognitive behavioral therapy and aerobic exercise provide only modest relief from symptoms in GWS (8,9).

Unexplained cases of GWI have been proposed to be due to subleathal exposures to chemical, biological and radiological substances (6). For example, inhalation of subclinical doses of sarin, a powerful organophosphorus nerve agent that has been shown to suppress T cell responses in rats (10), has been suggested as a etiological factor for some GWI cases (10). In contrast, Bregenholt et al. were unable to reveal any difference in natural killer cell function or T-cell cytokine production in 686 Danish Gulf War personnel, compared to 231 gender and age-matched healthy controls (11). Likewise, Everson and colleagues studied functional abnormalities in antigen presenting cells, T cells, T helper type 1 cells, T helper type 2 cells,

and B cells, and found no evidence for abnormal immunological responses in 52 symptomatic American Gulf War veterans, compared to 31 asymptomatic Gulf War veterans and 21 veterans who had applied for disability compensation and had not participated in the Gulf War (12). In addition, exposure to infectious agents, chemical warfare agents, vaccines, and environmental pollutants have been put forward as hypothetical etiological basis for GWI (6,13). A high prevalence of *Mycoplasma spp*. (around 50%) has been consistently reported in various samples of GWI patients (14-16). Analysis of Gulf War veterans and their immediate family members indicates that GWI cases have an increased risk of infection with *Mycoplasma spp*. (odds ratio = 17.9, 95% CL 4.1-78.1, $P<0.001$) as well as their symptomatic family members (odds ratio = 16.9, 95% CL 6.0-47.6, $P<0.001$) (17).

Some GWI patients may have also been exposed to depleted uranium (DU) (6). Schröder et al. (13) studied sixteen British war veterans (thirteen of whom were deployed in the 1990 Gulf War, two veterans of the Balkan War, and one veteran of both wars) and 40 healthy volunteers. All veterans were reported to suffer from various medical complaints since then, and they described situations during their tour of duty that were likely associated with DU exposure. DU can enter the human body through inhalation, ingestion, dermal contact, or injury, and soluble uranium is excreted preferentially by the kidneys, which may explains its nephrotoxicity (13). Incorporated DU causes exposure of the human tissues to ionizing radiation, which the researchers hypothesized to may have caused unstable chromosome aberrations. Standard peripheral lymphocyte metaphase preparations of patients and controls were examined for unstable rearrangement aberrations, namely dicentric chromosomes, centric ring chromosomes, and sister chromatid exchanges. According to the authors, these are considered valid and reliable biomarkers for previous exposure to ionizing radiation. Nevertheless, these assays are unable to reveal the exact source of ionizing radiation. The number of both the acentric fragments and chromatid aberrations were statistical significantly elevated in the veteran's group, while a statistical significantly lower frequency of sister chromatid exchanges were seen in the veterans compared to the control groups. It was concluded that these data provide strong evidence for previous exposure to ionizing radiation in at least 50% of the sample of veterans examined sample.

Although compelling, these results should be interpret with some caution. Since the authors studied a small sample of convenience, the ability to extrapolate these results to all deployed soldiers is limited. Second, the exact source responsible for the observed chromosome aberrations in this sample of (mainly Gulf) war veterans, cannot be attributed to DU. The fact that all veterans described situations during their tour of duty that were likely associated with exposure to DU does not alter that notion. Indeed, the authors themselves indicated that it is now widely accepted that the Gulf War veterans, as well as the Balkan veterans, were exposed to a large number of different toxic agents besides DU (e.g. pesticides, immunizations, etc.). Evidence for DU has been found in selected soil samples from at least some sites of the 1999 Balkan conflict (18). In addition, in another study approximately one-half of GWI patients were found to have fragile chromosomes that are more easily degraded by cellular nucleases, resulting in release of characteristic nucleotide fragments (19). A major source of chromosome damage could be from genotoxic materials released by intracellular infectious agents, such as *Mycoplasma fermentans* (20,21). If this is the case, then immediate family members with such infections may also show increased rates of chromosome damage.

Finally, evidence addressing the clinical importance of the chromosome aberrations in GWI patients is lacking. It would have been of interest to know whether the patients without evidence of chromosome aberrations presented with a different symptom pattern of illness or

less severe sign and symptoms compared to those who did. Still, the Schröder et al. study (13) provided new insights into a complex illness, provided new evidence supporting the biological nature of GWI, and generates important questions for future research.

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