



Committee on Veterans' Affairs

Subcommittee on Benefits

United States House of Representatives

October 26, 1999

Invited Testimony by Claudia S. Miller, M.D., M.S.

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I have been asked to explain how physicians who see sick Gulf War veterans can observe the same or similar symptoms and interpret them as either undiagnosed illness or diagnosed illness. Even when doctors apply monikers to these patients' illnesses, like depression, migraine headaches, asthma, irritable bowel or fibromyalgia, these monikers do not explain *why* these veterans are sick. Most have symptoms involving several organ systems simultaneously. For them there is no unifying diagnosis offered, no etiology specified, and no disease process clarified.

In truth, all of these veterans are undiagnosed because what we are dealing with is an entirely new mechanism of disease not covered by standard medical diagnoses -- one which presents itself symptomatically as different conditions to different specialists.

The rheumatologist observing diffuse muscle pain diagnoses myalgias.

The neurologist hearing head pain and nausea diagnoses migraine headaches.

The pulmonologist finding airway reactivity diagnoses asthma.

The psychiatrist seeing chronic malaise diagnoses depression.

The gastroenterologist noting GI complaints diagnoses irritable bowel syndrome.

Some private practitioners diagnose multiple chemical sensitivity, or MCS, which is not a diagnosis in itself, but rather just another manifestation of the underlying disease process.

So what is at the core of this myriad of symptoms that has come to be called "Gulf War Syndrome?" What is the underlying disease process? The key is in the new-onset intolerances these people share.

Over the past six years, I have served as a consultant to the VA's referral center for Gulf War veterans in Houston. The vast majority of the veterans there reported multiple new intolerances since the War. Among the first 59 patients, 78% reported new-onset chemical intolerances; 40% experienced adverse reactions to medications; 78% described new food intolerances; 66% reported that even a can of beer made them feel ill; 25 percent became ill after drinking caffeinated beverages; and 74 percent of smokers felt sick if they smoked an extra cigarette or borrowed someone else's stronger brand. More than half reported new intolerances in all three categories -- chemical inhalants, foods, and drugs or food/drug combinations.

One mechanic said that before the Gulf War his idea of the perfect perfume was WD-40. Since the war, WD-40 and a host of other chemicals make him feel ill. Many veterans no longer fill their own gas tanks because the gasoline vapors make them "spacy" or sick. Some won't drive because they become disoriented in traffic and they fear causing an accident. Or they can't find their cars, forget where they are going or get lost in once familiar areas. One VA study found excess motor vehicle deaths among Gulf veterans and interpreted this as possible increased risk-taking behavior (Kang and Bullmann, 1996). What the veterans tell me is that they get confused, go off the road, mistake the accelerator for the brake, and have trouble judging stopping distances when they are exposed to gasoline, diesel exhaust, or freshly tarred roads.

Researchers at the Robert Wood Johnson Medical School in New Jersey and at the University of Arizona have noted similar multi-system symptoms and intolerances to common chemicals, foods, and drugs among the veterans (Fiedler et al, 1996; Bell et al, 1998). And a CDC study found that ill Gulf War veterans reported more chemical intolerances than healthy veterans (Fukuda et al, 1998).

These studies are confounded by a phenomenon called "masking," which occurs when people become intolerant to many different things (Miller and Prihoda, 1999a). As they go through a day, symptoms triggered by fragrances, hairspray, vehicle exhaust, foods and medications pile up so they feel sick most of the time. No one cause can be isolated because there's too much background noise, and patients often underestimate the number of exposures that affect them.

This problem is not altogether new. German researchers described similar intolerances in chemical weapons workers after World War II (Spiegelberg, 1961). Nearly 20 percent of agricultural workers on a California registry for organophosphate pesticide poisoning (Tabershaw and Cooper, 1966) reported that even a "whiff" of pesticide made them sick with symptoms like those of the Gulf War veterans, as did dozens of government workers a decade ago, after the EPA headquarters became a "sick building" following remodeling (EPA, 1989). Similar outbreaks of chemical intolerances have been reported in more than a dozen countries (Ashford et al, 1995).

These observations suggest that we may indeed be dealing with an entirely new mechanism for disease, one which has been referred to with the acronym "TILT", or "Toxicant-induced Loss of Tolerance" (Miller, 1996, 1997, 1999). Any one toxicant appears capable of initiating this process. TILT involves two steps, initiation and triggering (Ashford and Miller, 1998): (1) First, a single acute or multiple low-level exposures to a pesticide, solvent or other chemical causes loss of tolerance in a subset of those exposed; (2) Thereafter very low levels of common substances can trigger symptoms -- not only chemicals, but various foods, medications, alcoholic beverages and caffeine. Symptoms involve several organ systems. These intolerances are the hallmark of TILT, just as fever is the hallmark symptom of infectious diseases.

Over the past several years, the finger has been pointed at a number of potential causes for Gulf War Syndrome -- everything from the oil shroud to pesticides, vaccinations, and pyridostigmine bromide. What set off the Gulf War Veterans? The answer is "all of the above." Exposure to any one or any combination of these toxicants may, in fact, be capable of causing a general breakdown in tolerance that can result in a plethora of beguiling symptoms.

We do not know exactly how this breakdown in tolerance occurs. We do know that rats with nervous systems sensitive to organophosphate pesticides are also intolerant of diverse drugs and have increased gut permeability which in humans is associated with food intolerance (Overstreet et al, 1996). This suggests the breakdown might involve the cholinergic nervous system, which regulates processes throughout the body.

How can these people be helped? No one knows -- yet. The biggest obstacle is the symptoms themselves, which serve as red herrings, diverting attention away from the central problem. What we do know is that Gulf War veterans, who have come to recognize what sets them off and then avoid these triggers, tend to improve. We need to apply this understanding to the diagnosis and treatment of other such veterans.

The first thing that needs to be done is to set up *unmasking* studies in which sick Gulf War veterans can be isolated from the exposures that are setting them off. This can be achieved by putting them in a special environmentally controlled hospital unit (Miller, 1997; Miller et al, 1997). Once we get them to baseline, we can reintroduce things like caffeine, perfumes, various foods, etc., and identify some of the things that cause their flare-ups. With avoidance, it is hoped that they, too, can improve. This combined diagnostic-therapeutic approach would eliminate much of the confusion that is the focus of this hearing.

There is no simple answer to Gulf War illness. No single toxicant is likely to have caused it. But if we concentrate less on the original toxicants and more on the underlying disease mechanism, I believe we can make progress in understanding why these people are sick and what we can do to help them.

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BIOSKETCH

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Other support related to these proceedings: Dr. Miller has served as a consultant to the Houston VA Regional Referral Center for Gulf War Veterans since 1993. She is also principal investigator on a study of neurobehavioral sensitization funded by the Office of Naval Research.

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