The Committee recommends that the federal government expand research efforts to systematically investigate the chronic effects of exposure to neurotoxins encountered during the Gulf War. Specifically, the Committee recommends that VA:

• Establish a comprehensive research program to investigate persistent and/or delayed effects of exposure to AChEi, including sarin and other nerve agents, at dosages comparable to those that may have been encountered in the Gulf War. Such research should focus on elaboration of the specific physiological pathways involved in possible adverse consequences of these exposures, including those involved in synergistic effects of combinations of neurotoxic exposures.

• Work with scientists with appropriate expertise to comprehensively evaluate the role of differences in genotype and activity levels of enzymes such as paraoxonase, acetylcholinesterase, and butyrylcholinesterase, which are associated with the uptake and metabolism of neurotoxins, in susceptibility to wartime exposures and the development of Gulf War veterans' illnesses.

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Acetylcholinesterase (AChE) and Gulf War illness. A number of chemical exposures in the Gulf War theater acutely reduce serum and brain levels of acetylcholinesterase (AChE), but only one study has assessed AChE measures in relation to Gulf War illness. Research in other populations has shown that individuals chronically exposed to low-level pesticides or stress express increased levels of the AChE read-through variant, AChE-R.1024,1418,1448 Based on these reports and early indications of possible treatment implications424,1446,1447 the Committee suggested that VA assess levels of AChE-R in eterans with Gulf War illness. VA Office of Research and Development subsequently authorized a study to determine whether AChE enzyme activity, more generally, was associated with anxiety and mood disorders in Gulf War veterans previously evaluated in the Iowa clinical study. Investigators later attempted to accommodate the Committee's original suggestion by adding an evaluation of AChE-R in relation to Gulf War illness to the study, but this was not accomplished because of insufficient serum.

Instead the study focused on AChE enzyme activity in relation to Gulf War deployment, as well as anxiety disorders and multisymptom illness in Gulf War veterans.266 Study results indicated that Gulf War deployment, overall, was not associated with significant differences in AChE activity. Mean value of AChE activity for veterans with chronic multisymptom illness (CMI) was nonsignificantly higher than in veterans who did not have CMI. For all veterans combined (sick and healthy), AChE activity was not significantly associated with any self-reported exposures during deployment. Veterans who reported exposure to chemical warfare agents, however, had an adjusted mean activity level that was 126 points lower than those not exposed, a difference that approached significance (p=0.09).266 As previously described, results of this study are difficult to interpret. Both Gulf War illness cases and controls had originally been recruited for a study of depression, fibromyalgia and cognitive dysfunction, and study subjects, overall, had elevated rates of anxiety disorders. Further, the study did not evaluate ssociations between AChE and Gulf War illness in veterans with different exposure histories, particularly AChE-nhibiting chemicals. The Committee therefore concludes that the question of whether AChE variability is associated with Gulf War illness has not been adequately addressed, and so remains open.

Additional Clinical and Research Findings Associated with Gulf War Illness

As described throughout this section, a variety of studies have identified biological measures that distinguish veterans with Gulf War illness from healthy controls. The areas of research already described have included multiple studies focused on different biological characteristics of symptomatic veterans. Most positive findings were obtained using research protocols that compared groups of symptomatic Gulf War veterans to healthy controls. Few of the identified Gulf War illness-related differences or abnormalities—whether related to the central nervous system, autonomic function, neurotoxicantneutralizing enzymes, endocrine parameters, or immune perturbations—were identified with diagnostic tests routinely used in clinical practice.

There is comparatively little information on other types of biological processes or objective measures in relation to Gulf War illness. The limited information available comes primarily from two sources: (1) reports describing clinical findings from specialty evaluations such as rheumatologic or gastrointestinal workups, and (2) results from single studies that have evaluated particular issues, such as pain sensitivity or the burning seminal fluid problem reported by veterans and their spouses.