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## CONCLUSIONS AND RECOMMENDATIONS

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### CONCLUSIONS

Four broad conclusions can be drawn from this review. First, a militarily effective dose of any of the agents considered in this review would not have escaped notice. Such a dose would have produced symptoms requiring treatment or would have killed the soldiers exposed. While there might have been some difficulty identifying a specific agent, no symptoms consistent with exposures to large doses of any of the agents included in this review were reported. One individual was apparently exposed to mustard gas residual.

Second, low-level exposures to many of these agents could have produced symptoms that were simply overlooked or attributed to other, more commonplace sources, such as irritation from dust and sand, upper respiratory infections, gastroenteritis, asthma, or the flu. The possibility of exposures to low levels of more than one agent either simultaneously or in relatively close proximity makes diagnosis difficult. Therefore, on clinical grounds alone, it is not possible to dismiss low-dose exposures to one or more of the agents or the possibility that such exposures contributed to some of the symptoms experienced by the Gulf War veterans. That said, it is difficult to accept that exposures affecting large numbers of troops would have escaped clinical notice. Furthermore, the literature reports no clinical symptoms developing years after exposure, which was the case for about half of the veterans reporting health problems.

Third, the literature suggests that some interaction may occur between chemical warfare agents and other factors. Several factors, such as stress, PB, and anticholinesterase nerve agents, that may contribute to the symptoms seen in the veterans can activate regulatory genes (such as *c-fos*) in the brains of animals. Because of the potential long-term effects of these genes, this observation may be important. However, the long-term effects in animals and the clinical significance for humans remain to be determined. Epidemiological studies of illnesses in the veterans might consider the possibility of aggregate effects.

Since mustards, trichothecene toxins, and nerve agents also inhibit AChE, it may be useful to examine their effects on regulatory gene expression as well.

Fourth, very little of the literature treats long-term effects of exposures to doses below those that would cause acute clinical symptoms. Considerably more research is needed in this area before even preliminary suppositions can be formulated.

## RECOMMENDATIONS

The primary recommendation is that research be conducted to fill the gaps noted here. The most obvious area needing additional research is the health effects of low-level exposures to agents or toxins. We would note that, since the Gulf War, DoD and the VA have begun to fund a good deal of research. Research in other areas would also be beneficial, including the following:

- understanding the effects of mustard agents on the central nervous system
- long-term follow-up studies on the Japanese exposed to sarin in the subway attack, particularly those exposed to low levels
- better understanding of the acute respiratory toxicity of aflatoxin in non-human primates
- research to determine the long-term effects of converging cholinergic activation of c-fos
- follow-up study of the duration of response of the convergent response mechanism of nerve agent action that Kaufer et al. (1998) described
- extension of the observations pertaining to the downregulation of nicotinic receptors in the brain from low-dose DFP
- making those involved in the epidemiological studies of accidents during and immediately after the Gulf War aware of the observation that sarin workers who had mild exposures were noted to have many industrial and vehicular accidents.

Finally, interactions between the various chemical warfare agents and other chemicals on the battlefield, as well as other psychosocial factors, such as stress, will need to be examined to develop a more complete understanding of the possible health consequences of exposure to chemical and biological warfare agents.