

Many Gulf War illnesses may be autoimmune disorders caused by the chemical and biological stressors pyridostigmine bromide, and adrenaline

J. I. Moss

Gainesville, Florida, USA

Summary Gulf War-related illnesses are mostly common ailments, but with incidence rates that exceed those expected in the population of Gulf War veterans. These illnesses may be the result of combinations of chemical and physiological stressors which may have caused acute cellular effects sufficient to initiate processes of autoimmunity to various organs, tissues or types of cells. Two main suspects in the Gulf War cluster of illnesses are the 'Nerve Gas Pill' (pyridostigmine bromide, PB, NAPS) and stress. One component of stress, β -adrenergic load, potentiates the toxicity of PB. While similar types of chemical and physiological stressors are present in the general population, the Gulf War veteran population received these stressors in a short time, with greater intensity, and at a higher percentage exposure than normal for the general population. This may be an opportunity to learn the cause, how to prevent, and, possibly, how to treat these ailments in Gulf War veterans and in the general population.

© 2001 Harcourt Publishers Ltd

SOME GULF WAR EXPOSURES MORE LIKELY AT DAMAGING LEVELS THAN OTHERS

Haley and Kurt (1) suggested that two of three major syndromes identified by them which resulted from Gulf War service, were the product of exposure to pyridostigmine bromide (PB) in combination with either 'perceived chemical weapons exposure' or a government-issued insect repellent containing 75% DEET (N,N-diethyl-m-toluamide).

I have suggested that one of the most prominent 'exposures' in the Gulf War (PB) may produce an unexpected outcome if the drug were taken under conditions that were different than those in place during the testing and evaluation of this drug for nerve gas prophylaxis. I

have also suggested that the pharmacology of the PB-DEET interaction should be explored in detail so that the effect(s) of altered toxicity of PB by DEET could be evaluated on a molecular level (2–6) to possibly reveal other conditions that might alter the outcome of PB exposure.

The pharmacology of DEET may resemble that of some adrenergic drugs (3–5) and the perception of nerve gas exposure is likely to alter the adrenergic load of the perceiver. The demonstrated potentiating effect on PB toxicity by beta-adrenergic load (4,5) therefore becomes a possible substitute for the combinations of PB plus DEET, and PB plus a 'perception of nerve agent exposure'. In light of the lack of evidence for any pharmacologically active level of nerve gas exposure during the Gulf War, it might be more realistic to substitute adrenaline for nerve gas (and possibly DEET) as a PB synergist and consider whether there is any plausible, mechanistic, reason to favor one 'cause' of Gulf War illnesses over the other. If none can be found, it may be useful to first attempt to understand the consequences of synergistic exposures that are most likely to have taken place in a large

Received 5 January 2000

Accepted 20 March 2000

Correspondence to: James I. Moss, Gainesville, Florida USA

E-mail: jimmos@cox.net

proportion of the Gulf War veteran population. PB and adrenaline 'exposures' were:

1. Near levels that should be expected to have fairly profound physiological effects.
2. These 'exposures' were often likely simultaneous, because PB was taken in anticipation of nerve gas attacks, with apparent knowledge of such possible attacks.
3. Both are 'chemicals' which potentiate each other's effects (4–6).

PB and adrenaline 'exposures' during the Gulf War appear to satisfy all these conditions more closely than other potential exposures during the Gulf War.

MINOR EFFECTS OF A SUBSTANCE MAGNIFIED BY SYNERGISM

PB could reasonably be dismissed as a 'cause' of Gulf War illnesses because transient, sub-lethal, cholinesterase inhibition is not commonly thought to cause chronic disease. Organophosphate chemicals have been given more credibility because of their known ability to inhibit longer, and inhibit enzymes other than cholinesterase. However, irreversible enzyme inhibition by PB could be mimicked by continual dosing, as was done in the Persian Gulf. Also, serene hydrolytic enzyme inhibitors such as PB often inhibit other enzymes of the same type, in addition to acetyl cholinesterase, the enzyme that is considered the primary target of the compound. Under controlled conditions, such 'secondary' effects may be masked by the known action of the drug. However, potentiation of such secondary effects by chemicals (synthetic or physiological), could increase one effect and not the other, and thereby turn 'secondary' effects into primary effects.

POSSIBILITY OF CHEMICALLY INDUCED AUTOIMMUNITY

The 'mystery' with Gulf War illnesses is not so much whether potentially toxic exposures occurred, but how this could translate into known chronic, diagnosable diseases, as seen in many of the studies on Gulf War illness (7). Few obvious mechanisms are in place that can explain such chronic diseases. Close associations between the illnesses and occult infections, direct and immediate damage to parts of nervous and endocrine organs, and slowly progressing tumors in nervous and endocrine tissues have yet to be reported. Autoimmune diseases are more difficult to sort out.

In light of indications (8–10) and hypotheses (11,12) of immune dysfunction in Gulf War veterans, it might be prudent to consider the possibility that autoimmune

processes are at work in at least a significant proportion of our Gulf War veterans.

The genesis of autoimmune diseases is not yet clear. However, a limited number of models suggest that chemical exposures could play a role. The outcome is known: antibodies recognize self proteins as foreign. A 'self' protein may be recognized as foreign by more than one mechanism.

One commonly cited way for this to happen is by 'molecular mimicry', in which a pathogen's protein is similar enough to a native protein that the immune system mounts an offensive against the foreign protein and later attacks self proteins. A version of this molecular mimicry can be easily envisioned in a case where a native protein is chemically modified, is recognized as foreign, and the same process as 'classical' molecular mimicry takes place. In this model, the immune system would later turn to the 'similar' (chemically NOT modified) protein(s). Both models may require epitope spreading and other processes, but there need be no differences in these two mechanisms once the first 'recognition' takes place. The chemical modification of the native protein need not be covalent or irreversible, only sustained, as would be seen in a prolonged exposure, as with PB in the Persian Gulf.

Another possible way for a native protein to be recognized as foreign is for a self protein to be presented to the immune system after the immune system had matured and 'self recognition' had been eliminated or suppressed. One possible way to do this is to cause cellular damage so that the internal proteins are more available to immune system contact. In this case, any type of action that caused the destruction or serious disruption of the integrity of cells (not necessarily all, or even enough of the cells to cause gross acute symptoms) would expose the 'foreign' parts of cellular proteins and this could lead to the initiation of subsequent autoimmune disease. The immune attack on internal parts of cells may seem counterintuitive because of limited access, but this appears to be the outcome of Type I diabetes, regardless of the initiating factors.

DIABETES MODEL

A diabetes model has served as an example of another possible mechanism to autoimmune disease. This has been called the 'Bystander Effect'. In this model, an extension of the above-mentioned result from cellular damage, autoimmunity may result from 'bystander' T-cell activation resulting from viral damage to cells, instead of by molecular mimicry. In one case (13), the Cocksackie B4 virus (which has been associated with the development of insulin-dependent diabetes mellitus in humans), is thought to mimic the native protein (glutamic acid decarboxylase) and thereby cause diabetes. In Cocksackie B4

virus-infected mice, those with a T-cell receptor transgene specific for a different islet cell autoantigen (not glutamic acid decarboxylase), developed diabetes. In short, the Coxsackie B4 virus-infected mice developed diabetes, but the antibodies were to other cell proteins, not the one that the virus has been reported to mimic. This was interpreted to indicate that cell damage and other effects on islet cells by the virus, and not molecular mimicry of the eventual antigenic protein, initiated the autoimmune destruction of the islet cells, and the resulting diabetes. In this model of autoimmune induced diabetes, chemical damage to islet cells might produce the same result.

There are many tissues, organs, and organ systems, in addition to neural tissues, that are potential targets of co-synergism between PB and some pesticides, drugs, and stress-mediating biochemicals such as adrenaline (review in 6). Mechanisms of cellular damage-induced diabetes could apply to other autoimmune diseases, which affect other tissues or organs.

MULTIPLE SYMPTOMS IN AUTOIMMUNE ILLNESS COULD BE FROM IDENTICAL EXPOSURES

Overlapping multi-system, multi-organ illnesses that seem diffuse and hard to pin to a single cause, may simply be the response one would expect the immune system to produce when numerous tissues were damaged or affected by a relatively small number of chemicals or other 'causes'. The process that produces antigen receptors (antibodies) is a fairly random 'shuffling of the deck'. People's immune systems may or may not have antibodies to specifically modified or previously 'hidden' protein epitopes. Antibodies that do happen to recognize self, will often see another 'part' of 'self', because of the partially random nature of antibody production. Some variation in symptoms need not indicate various causes.

Much of the above is within conventional biomedical knowledge. Debates over 'new syndrome' vs. 'no new syndrome' detract from the important questions about Gulf War illnesses which might be better directed to 'Why are so many sick?' and 'How do we treat and prevent recurrences?' One substance, PB, was consumed at levels much closer to toxic levels than any others likely present in the Persian Gulf, except, possibly, 'stress'. And one stress response mediator, adrenaline, increases PB toxicity. If autoimmunity does turn out to be a major problem with Gulf War veterans PB, combined with stress-mediating chemicals such as adrenaline, should be high on the list of suspected causes.

In the aggregate, no widespread 'new' illness has yet been clearly documented in Gulf War veterans (7) in spite of increases in 'normal' illnesses. We could dismiss Gulf War-related illnesses as simply elevated incidences of common illnesses. On the other hand, we could see the situation as a rare opportunity to work toward the prevention and treatment of disease(s) that affect countless millions of people and needlessly sap precious resources worldwide.

REFERENCES

1. Haley R. W., Kurt T. L. Self-reported exposure to neurotoxic chemical combinations in the Gulf War. A cross-sectional epidemiologic study. *JAMA* 1997; **277**: 231–237.
2. Is Military Research Hazardous to Veterans' Health? Lessons from World War II, The Persian Gulf, and Today. Hearings before the US Senate Committee on Veterans' Affairs, 103rd Cong, 2nd Sess, May 6 1994.
3. Moss J. I. Synergism of Toxicity of N,N-Diethyl-m-toluamide to German cockroaches (Othoptera: Blattellidae) by hydrolytic enzyme inhibitors. *J Econ Entomol* 1996; **89**(5): 1151–1155.
4. Chaney L., Moss J., Mozingo J., Hume A. Toxic interactions between pyridostigmine (PB), N,N-Diethyl-m-toluamide (DEET), adrenergic agents and caffeine. *Toxicologist* 1997; **36**(1), P2, p21, #106.
5. Chaney L. A., Mozingo J. R., Hume A. S., Moss J. I. Potentiation of pyridostigmine bromide toxicity in mice by selected adrenergic agents and caffeine. *Vet Human Toxicol* 1997; **39**(9): 214–219.
6. Moss J. I. Possible Potentiation of Pyridostigmine Bromide (PB) by Pesticides (p. 181–193). In: Report of the Special Investigation Unit on Gulf War Illnesses, Committee on Veterans' Affairs, United States Senate 1998 (September); S. Prt. 105–139. (<http://www.senate.gov/~veterans/siu.htm>)
7. Murphy F., Kang H., Dalager N., Lee K., Allen R., Mather S., Kizer K. The health status of Gulf War veterans: lessons learned from the Department of Veterans Affairs Health Registry. *Mil Med* 1999; **164**(5): 327–331.
8. Rook G. A., Zumla A. Gulf War syndrome: is it due to a systemic shift in cytokine balance towards a Th2 profile? *Lancet* 1997; **349**(9068): 1831–1833.
9. Grady E. P., Carpenter M. T., Koenig C. D., Older S. A., Battafarano DF. Rheumatic findings in Gulf War veterans, Abstracts – February 23, *Arch Intern Med* 1998; **158**: 367–371.
10. Zhang Q., Zhou X. D., Denny T., Ottenweller J. E., Lange G., LaManca J. J., Lavietes M. H., Pollet C., Gause W. C., Natelson B. H. Changes in immune parameters seen in Gulf War veterans but not in civilians with chronic fatigue syndrome. *Clin Diagn Lab Immunol* 1999; **6**(1): 6–13.
11. Doucet I. Desert Storm syndrome: sick soldiers and dead children? *Med War* 1994; **10**(3): 183–194.
12. Everson M. P., Kotler S., Blackburn W. D. Jr. Stress and immune dysfunction in Gulf War veterans. *Ann N Y Acad Sci* 1999; **876**: 413–418.
13. Horwitz M. S., Bradley L. M., Harbertson J., Krahl T., Lee J., Sarvetnick N. Diabetes induced by Coxsackie virus: initiation by bystander damage and not molecular mimicry. *Nat Med* 1998; **4**(7): 781–785.