as scavengers of a given inhibitor is unknown. Moreover, blood scavengers do not necessarily mirror the whole-body detoxifying ability. In particular, there is no evidence in humans for a major role of plasma BuChE in the detoxification of pyridostigmine. As a matter of fact, data (enzyme concentration and resynthesis, rates of inhibition and spontaneous reactivation) suggest that AChE may also be a scavenger for pyridostigmine and perhaps a better scavenger than BuChE.

The so-called 'unexpected illness' reported in several veterans after service in the Persian Gulf War is an ill-defined syndrome not entirely attributable to cholinergic overstimulation[4], as indeed is the case for the patient described by the authors. Moreover, clinical signs and symptoms of pyridostigmine poisoning are short-lived after cessation of treatment, as expected for a reversible AChE inhibitor. Therefore the authors' comments concerning the possible long-term adverse effects of pyridostigmine should be reconsidered.

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Soreq replies — Our primary goal in presenting this case study was to make the biomedical community aware of the potential for complications of anticholinesterase therapies when they are applied to 'atypical' butyrylcholinesterase (BuChE) subjects. The current use of the anti-cholinesterase tacrine for treating Alzheimer's disease patients is a good example of such danger, and genotype–phenotype tests of patients who respond adversely to tacrine should clarify the extent of this problem. Presumably Drs Lotti and Moretto share our view of this particular issue with respect to the use of tacrine given that they offer no criticism of our tacrine data. However, our attention was drawn to the drug-scavenging role of blood BuChE because of the experience, during the Persian Gulf War, of the pyridostigmine-treated 'atypical' BuChE soldier on whom we reported. To us, this suggested that a genetic variation in BuChE may have caused differences in scavenging for pyridostigmine as well as for succinylcholine. Our report is certainly not the final word on a subject that should be investigated in more subjects who experienced bad responses.

Inhibited blood BuChE can potentially be replaced much faster than the 120-day lifetime of erythrocyte acetylcholinesterase (AChE). We therefore view BuChE as a better candidate than AChE for an *in vivo* scavenging role, in spite of the difficulty in extrapolating *in vitro* data to an *in vivo* situation in the absence of complete data on enzyme turnover. Moreover, although it is not known how much of the blood BuChE is available for drug interactions, 'atypical' BuChE would certainly be much less effective in such interactions. However, as is clear from our paper, we have never subscribed to the notion that the only physiological role of BuChE is that of a scavenger. Moreover, we certainly agree that the genetics of BuChE does not fully explain the Gulf War syndrome. One of the reasons for the vague definition of this syndrome may be the numerous as-yet-unexplained short- and long-term connections between cholinergic circuits and changes in various motor, sensory and cognitive functions. If our recent contribution will elicit more interest and further research on these issues, it has indeed reached its goal.

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1. Loewenstein-Lichtenstein, Y. *et al.* Genetic predisposition to adverse consequences of anticholinesterases in 'atypical' BCHE carriers. *Nature Med.* **1**, 1082–1085 (1995).
2. Gilman, A.G., Goodman, L.S., Rall, T.W., Nies, A.S. & Taylor, P. *Goodman and Gilman's The Pharmacological Basis of Therapeutics*, 8th edn (Pergamon, New York, 1990).
3. Reiner, E. & Lotti, M. Enzymes interacting with organo-phosphorus compounds. *Chem. Biol. Interact.* **87**,1–476 (1993).
4. National Institutes of Health. The Persian Gulf Experience and Health. *NIH Technol. Assess. Statement* Apr. 27–29, 1–12 (1994).

Taking tamoxifen to heart

To the editor — Grainger and colleagues[1] suggest that the ability of tamoxifen (TMX) to suppress diet-induced lipid lesions in mouse aorta is related to its ability to elevate levels of transforming growth factor-β, which is thought to have a cardioprotective effect. However, it should be noted that TMX (and its more effective 4-hydroxy metabolite) is a potent antioxidant[2] and indeed can protect against the oxidative damage implicated in atherosclerosis. Furthermore, it is likely that TMX can accumulate in the artery wall to achieve the barely micromolar concentrations required for this effect[2,3]. Current studies are planned to examine the decreased susceptibility to oxidation of LDL isolated from TMX-treated women.

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Grainger replies — Although TMX may prevent lipid lesion formation by reducing LDL oxidation, this is unlikely to be responsible for the effects we reported. We have previously shown that changes in vessel wall structure marked by the presence of osteopontin occur at sites of depressed TGF-β activity even when mice are fed a low-fat diet[4]. It is these sites that go on to become fatty streak lesions when the mice are fed a high-fat diet. TMX prevents these vessel wall changes (and osteopontin expression) irrespective of the fat content of the diet[1]. Since mice do not have much LDL in circulation when fed a low-fat diet[1], reduction of LDL oxidation is unlikely to be responsible for these effects. It is much more likely that TMX acts to prevent changes in vessel wall structure that subsequently render the cells more prone to taking up lipid, than any direct effect on the lipid itself.

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1. Grainger, D.J., Witchell, C.M. & Metcalfe, J.C. Tamoxifen elevates transforming growth factor-β and suppressed diet-induced formation of lipid lesions in mouse aorta. *Nature Med.* **1**, 1067–1073 (1995).
2. Wiseman, H. Tamoxifen: New membrane-mediated mechanisms of action and therapeutic advances. *Trends Pharmacol. Sci.* **15**, 83–89 (1994).
3. Wiseman, H., Paganga, G., Rice-Evans, C. & Halliwell, B. Protective actions of tamoxifen and 4-hydroxytamoxifen against oxidative damage to human low-density lipoproteins: A Mechanism accounting for the cardioprotective action of tamoxifen? *Biochem. J.* **292**, 635–638 (1993).
4. Grainger, D.J. *et al.* Activation of transforming growth factor-β is inhibited in transgenic apolipoprotein(a) mice. *Nature* **370**, 460–462 (1994).