

- 5 Garrey SM, Voelker R, Berglund JA. An extended RNA binding site for the yeast branch point-binding protein and the role of its zinc knuckle domains in RNA binding. *J Biol Chem* 2006; **281**: 27443–53.

Pricing of orphan drugs

The *Lancet's* leader on solutions to the research and development crisis for neglected diseases (Nov 22, p 1784)¹ warns of a problem with the cost of orphan drugs, but this is already a reality.

An inherited defect of N-acetylglutamate synthetase was first described by Bachmann in 1981.² N-acetylglutamate is an allosteric activator of carbamyl phosphate synthetase, the first step in the urea cycle. The disorder is very rare, although more cases have been diagnosed since the gene was identified.^{3,4} Bachmann introduced treatment with N-carbamylglutamate in 1982.⁵ The treatment is highly effective and must be continued for life.

N-carbamylglutamate is now licensed as an orphan drug, but the price has risen sharply. The current price of the unlicensed product is £11 (US\$15) per g whereas the price of the licensed one is £262.90 (\$367.30) per g. If the licensed preparation is used, the annual cost for a 10 kg child increases from £4015 (\$5611) to more than £95 000 (\$132 774). The reasons for the high price are not clear. Since the compound was already being used for this purpose, albeit unlicensed, the expenditure on research and development must be less than developing a medicine from scratch. When questioned informally by one of us (JVL), a company employee cited the cost of licensing and the small number of patients being treated.

The price of N-carbamylglutamate is now so great that patients risk being denied full treatment. It is clear that a robust mechanism is needed to set the price of orphan drugs, otherwise patients will be the ultimate losers.

JVL no longer treats any patients but has used the unlicensed product in the past. He has received payment for planning and lecturing on courses organised by Orphan Europe. He acts as consultant to Swedish Orphan (UK) and Special Products Ltd. SR has used both the unlicensed and licensed products.

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- 1 The Lancet. Solutions to the R&D crisis for neglected diseases. *Lancet* 2008; **372**: 1784.
- 2 Bachmann C, Krähenbühl S, Colombo JP, Schubiger G, Jaggi KH, Tönz O. N-acetylglutamate synthetase deficiency: a disorder of ammonia detoxication. *N Engl J Med* 1981; **304**: 543.
- 3 Caldovic L, Morizono H, Panglao MG, et al. Cloning and expression of the human N-acetylglutamate synthase gene. *Biochem Biophys Res Commun* 2002; **299**: 581–86.
- 4 Caldovic L, Morizono H, Tuchman M. Mutations and polymorphisms in the human N-acetylglutamate synthase (NAGS) gene. *Hum Mutat* 2007; **28**: 754–59.
- 5 Bachmann C, Colombo JP, Jaggi K. N-acetylglutamate synthetase (NAGS) deficiency: diagnosis, clinical observations and treatment. *Adv Exp Med Biol* 1982; **153**: 39–45.

Gulf war illnesses

In your Editorial of Nov 29 (p 1856)¹ you repeat the conclusion of the “Binns committee” report, sponsored by the US Veteran’s Administration, to the effect that those who served in the 1991 Gulf war are at increased risk of ill health, and that it is unequivocally the result of exposure to pyridostigmine bromide and pesticides. The former conclusion is hardly new, and the latter is far from certain. We were the first to confirm, in this journal, that service in the 1991 Gulf war affected the subjective health of some UK service personnel,² even though this effect did not amount to a new illness per se.³

However, if either pyridostigmine bromide or pesticides were indeed associated with ill health, one would have expected a new “Iraq war syndrome” in UK Armed Forces as of 2003, since pyridostigmine bromide was again issued, and used, by 73% of UK forces during the invasion of Iraq, as it was in the 1991 Gulf war. Likewise, pesticides were again used

to combat the threat of insect-borne disease. Yet despite the use of both agents by UK personnel, we found no evidence that history did repeat itself.⁴

The evidence implicating organophosphate agents in the cause of ill health in UK military personnel who deployed to the Gulf is far from compelling. We have found no evidence of peripheral neuropathy in UK personnel.⁵

We agree with the Binns committee that psychological disorders are not the most plausible explanation for Gulf war illness. Given that there is no dispute that Iraq has proven to be a longer, harder, and more dangerous campaign than Gulf 1991, if frank mental health disorders were a major causative factor, then we would have found the opposite results to those that we reported.⁴

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- 1 The Lancet. Justice delayed: acknowledging the reality of Gulf War illness. *Lancet* 2008; **372**: 1856.
- 2 Unwin C, Blatchley N, Coker W, et al. Health of UK servicemen who served in Persian Gulf War. *Lancet* 1999; **353**: 169–78.
- 3 Ismail K, Everitt B, Blatchley N, et al. Is there a Gulf War syndrome? *Lancet* 1999; **353**: 179–82.
- 4 Horn O, Hull L, Jones M, et al. Is there an Iraq war syndrome? Comparison of the health of UK service personnel after the Gulf and Iraq wars. *Lancet* 2006; **367**: 1742–46.
- 5 Sharief MK, Priddin J, Delamont RS, et al. Neurophysiologic analysis of neuromuscular symptoms in UK Gulf War veterans: a controlled study. *Neurology* 2002; **59**: 1518–25.

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Macchiarini P, Jungebluth P, Go T, et al. Clinical transplantation of a tissue-engineered airway. *Lancet* 2008; **372**: 2023–In this Article (Dec 13), the affiliation for L E Rees, T A Cogan, and A Dodson should have been [School of Clinical Veterinary Science, University of Bristol, Bristol, UK](#).



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