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Select Committee on Defence Minutes of Evidence

Memorandum submitted by Professor Malcolm Hooper, Scientific Advisor to the Gulf Veterans' Association

NERVE AGENT PRE-TREATMENT SETS (NAPS)—PYRIDOSTIGMINE BROMIDE, PB

Pyridostigmine bromide, an old drug patented in 1951, is used almost exclusively for the treatment of *Myasthenia gravis*, an autoimmune disease, in which acetylcholine receptors in muscle, Figure 4, are progressively destroyed. It acts as a reversible inhibitor of acetylcholinesterase, AchE, an enzyme which destroys acetylcholine, Ach. Inhibition of AchE increases the level of Ach at the nerve-muscle junction and compensates, in the early stages of *Myasthenia gravis*, for the loss of the receptors which are responsible for onward transmission of the nerve impulse.

PB was subsequently investigated in animal studies as a protective agent against the nerve agent soman. This point is important on two counts—

1. Soman and related, organophosphate nerve agents, sarin, cyclosarin, VX are potent irreversible inhibitors of AchE. Irreversible inhibitors act over a long time and their effects are only overcome by the synthesis of new enzyme which takes days. To avoid total loss of AchE it was necessary to—

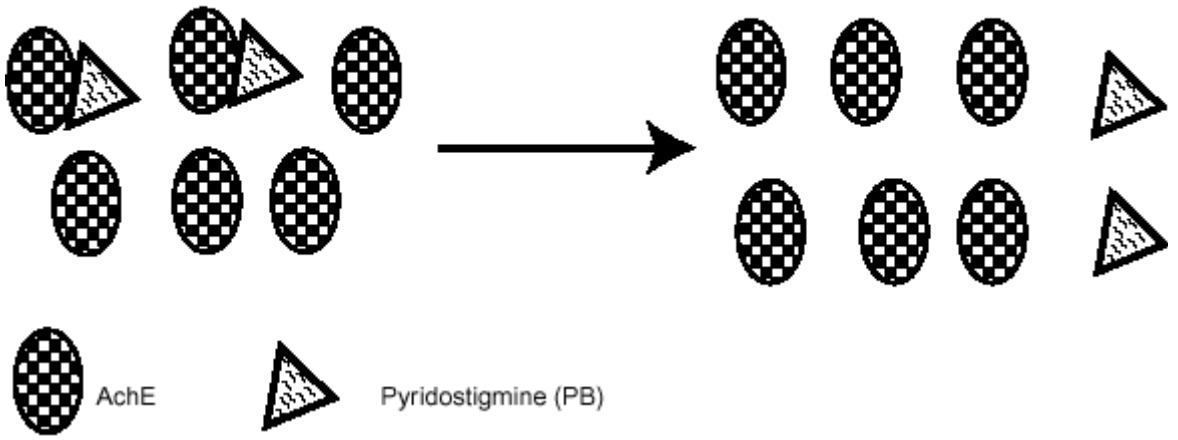
(a) find new drugs, which would need to be administered as soon as a chemical attack occurred, that would displace the nerve agents from their binding sites on AchE. Such a drug is pralidoxime, P2S. It was provided in "combopens" issued to the troops. [These also contained atropine, a potent anti-muscarinic drug, and avizafone, a pro-drug of diazepam see CWs below.]

(b) protect AchE by prior treatment, ie prophylactically, using a compound that prevents binding of the nerve agent to AchE.

2. Soman is particularly dangerous in that it "ages" AchE very rapidly and renders the enzyme insensitive to rescue by pralidoxime.

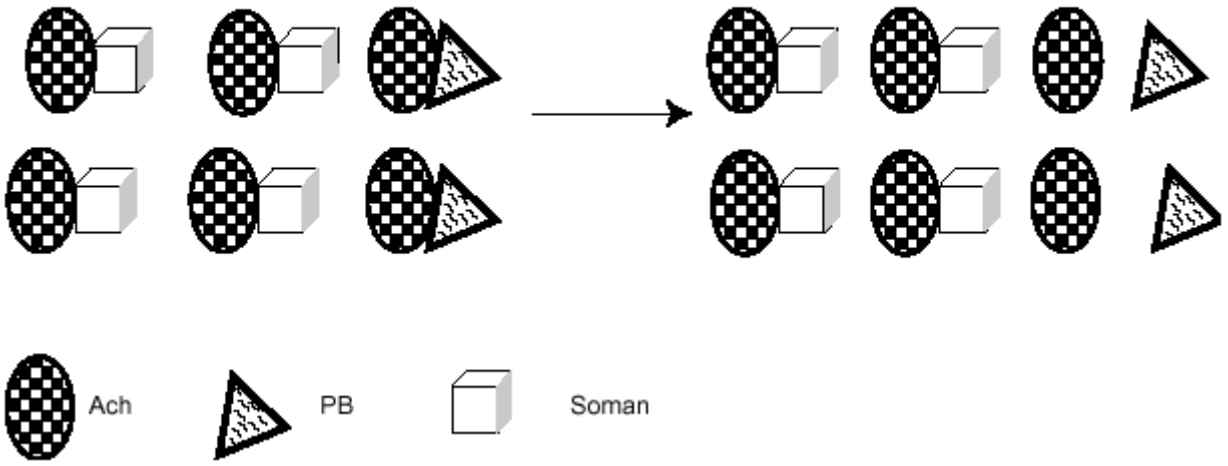
It was proposed that pyridostigmine bromide by binding reversibly would prevent the binding of soman to AchE. This would result in the gradual release of undamaged enzyme, as the PB-AchE complex dissociated, restoring a limited amount of normal function, Figure 6.

Figure 6: Reversible Inhibition of AchE by Pyridostigmine



Approximately 30 per cent of AchE is inactivated by the reversible binding of PB. When the drug is no longer at the calculated blood level the bound complex slowly dissociates restoring AchE levels to normal.

Figure 7: Binding of Soman and PB to AchE



An attack involving soman would lead to all the AchE being inhibited but slowly the AchE-PB complex would dissociate, if no further PB was taken, liberating free enzyme to restore some nerve function. However, administering PB whilst being exposed to any nerve agent would exacerbate and not relieve the symptoms/damage.

Such a strategy required two important judgements to be made—

(i) How much enzyme could be inhibited by PB without compromising the ability of troops to engage in warfare?

(ii) Which sites within the body needed to be protected?

This was completely new territory. No experimental data from human studies were available. The strategy was unproven. The use of PB would be experimental.

THE TROOPS WOULD BE USED AS GUINEA PIGS

It was decided to use a dose of PB, 30 mg eight-hourly, that would bind to 30 per cent of AchE. It was further assumed that PB, a quaternary compound would not enter the brain.

The strategy is fatally flawed—see also CWs antidotes and treatment, below.

If PB did not enter the brain then it would only protect AchE in the periphery and not in the brain! Any restoration of function would only be possible in the periphery. The recovery of battlefield casualties would be very unpredictable. They might die from the centrally mediate effects of nerve agents or survive as human "vegetables".

As for the assumptions. All the reports from troops taking PB describe the classic textbook symptoms of increased cholinergic stimulation —excessive sweating, lacrimation, salivary secretion, increased need to micturate and defaecate, lowered heart rate and force, respiratory problems from increased secretions, loss of muscle power, and disturbances of eyes, and the central nervous system.

It has now been demonstrated in experimental animals that the blood-brain barrier is breached when animals are stressed. Under these conditions PB might enter the brain. Increased central cholinergic effects have been found in troops, Sharabi *et al*, 1991 taking PB and in experimental stressed animals following administration of PB, Friedman *et al*, 1996, Kaufer *et al*, 1998.

There is considerable evidence of synergistic adverse effects arising from interactions between PB, OPs, DEET and permethrin which affect the entire nervous system, see Golomb, 1999 for a comprehensive review. This evidence appears in peer reviewed papers, several reports from the USA Congress, House of Representatives, and the final Presidential Commission.

In addition adverse synergistic interactions involving the cholinergic and the-adrenergic stress-response system have been reported, Chaney, 1997; Moss, 1998, 1999.

The recent Rand Report, Golomb, 1999, which includes 83 pages of references, concluded that,

(1) PB cannot be ruled out as a possible contributor to the development of unexplained or undiagnosed illness in some PGW (Persian Gulf War) veterans . . .

(2) Uncertainties remain concerning the effectiveness of PB in protection of humans against nerve agents . . .

(3) The use of PB may reduce somewhat the effectiveness of postexposure treatment for nonsoman nerve agents . . .

(4) The issue is a complex one, involving trading off uncertain health risks—but risks now shown to be biologically plausible—against uncertain gains from the use of PB in the warfare setting.

These rather cautious conclusions can be considerably strengthened in the light of the work assesed in the whole report and from consideration of related literature, particularly that concerning chronic exposure to insecticides and nerve agents.

Haley, 1997a, has found an association of PB with his Syndromes 2 (confusion ataxia) and 3 (arthro-myo-neuropathy).

CONCLUSION

My overall assessment of the evidence is that the choice of PB and its proposed use in the Gulf War was—

(1) An unproven strategy involving the use of troops as experimental subjects without their prior consent.

(2) The strategy was fatally flawed in that it will not protect the brain from exposure to nerve agents.

(3) The protocol adapted was based on two assumptions, on dosage and drug distribution, which later proved to be wrong.

(4) The synergistic adverse interactions between PB and other anticholinesterase drugs, particularly OP and carbamate insecticides, greatly exacerbated the injury to the central, peripheral, and autonomic nervous systems.

(5) The damage referred to in (4) above must be evaluated in the light of the growing knowledge of the chronic damage now recognised in OP poisoned animals, sheep farmers, and pesticide operatives.

(6) It is a shameful fact that there have been no studies, almost 10 years after the Gulf War, carried out in the UK which address these health issues despite irrefutable evidence from studies in the States.

(7) There is clear evidence that there is a toxic synergism between PB and adrenergic agents, caffeine, and stress, Chaney *et al*, 1997; Moss, 1999; and with insecticides, McCain *et al*, 1997.

(8) Opioid-cholinergic modulation of growth hormone, a major endocrine hormone, also occurs with PB, De Marinis *et al*, 1997.

(9) Acetylcholine also exerts an effect on the immune system which would be amplified by PB, Kuby, 1992.

(10) PB alters muscle sensitivity, Lintern *et al*, 1997; alters growth hormone responses, Nooitgedagt, 1997; especially in panic attack patients, Cooney *et al*, 1997.

(11) Causes severe damage in heart muscle probably by harmful effects on mitochondrial function, Glass *et al*, 1996, 1997.

(12) Extensive neurological studies are needed to evaluate the extent of damage suffered by many veterans. These must include MRI, SPECT, and PET scans of the brain, studies of the neuromuscular junction function and peripheral nerve conduction, assessment of the levels and properties of key enzymes, particularly paraoxonase, P-450 enzymes, acetylcholinesterases and butyryl cholinesterases.

NOTE—TAKING THE TABLETS

It is clear from accounts in the battlefield that PB tablets were taken erratically. Some troops took 30 mg three times daily whilst others took 60 mg three times daily. Some stopped using PB, whilst others increased the dose particularly when threatened with possible chemical exposures.

VACCINATIONS

The preparation for the Gulf War was done under considerable pressure and in fear of very heavy casualties. A vaccination programme was inaugurated in which a large number of vaccines were given, including those designed to counter the threat of biological weapons, BWs. Iraq was known to have a large range of biological cultures for such weapons which were supplied mainly from the USA, Reigle, 1994, Thomas 1998; see also under BWs section.

The UK preparation involved the administration of eight health and hygiene vaccines—typhoid, polio, hepatitis B, hepatitis A, cholera, tetanus, yellow fever, meningitis, plus two BW vaccines, anthrax with pertussis (this really is two extra vaccines and not one), and plague. Botulinum anti-toxin was prepared in large amounts and sent out to the Gulf to be used if troops were exposed to botulinum toxin. The Americans received 17 different vaccines which included additionally influenza, rabies, measles, Japanese B encephalitis virus, rubella, varicella, and botulinum toxoid, Specter, 1998.

Although some service personnel did not receive every one of these vaccines, eg hepatitis A immunoglobulins, it is generally admitted by the MoD that each soldier received up to 10 different vaccines.

However, some troops received additional known vaccines. We have the records of one veteran who received the controversial MMR, triple vaccine because he had no extant vaccination records when called up from the reserves.

In addition we know that the vaccination programme continued in the Gulf and that it was the policy of USA units to vaccinate everyone in their bases even if they were visiting Coalition personnel. In this way some UK troops received USA vaccines, Cammock, 1997.

Both the USA and UK Governments are believed to have given additional vaccines which were undeclared and unidentified on grounds of National Security; for example, smallpox and tularaemia (rabbit fever). Vice-Admiral Revell, the Surgeon General, stated before the Defence Committee, 1996, that some five or six vaccines had not been disclosed. A footnote to the report states that what this meant was five or six injections. Such a statement does not make sense since he was being asked about vaccines not injections. I find it difficult to believe that the Surgeon General does not know the difference between a vaccine and an injection.

Since it is now clearly established that the USA and UK sold cultures for biological weapons to Iraq we knew the types of BWs that Iraq might prepare. In this regard, smallpox is a favoured Russian biological agent (cf soman), and tularaemia had been developed and weaponised by the USA in 1971-73. Haemorrhagic viruses, also investigated in the USA as BWs, were released to Iraq.

RECORDS

It is common knowledge that most of the medical records detailing the vaccines given have been lost or destroyed. The destruction of records had been described as a matter of military policy! In the Lancet paper, by Unwin *et al,* 1999, some 70 per cent of Gulf personnel were found not to have their records. It is not possible, therefore, to make any categorical statements about which vaccines were given and when.

I am aware of Parliamentary reports which list 151 records that the MoD has available. These included two for smallpox and one for tularaemia. Scaled up to the 53,000 UK personnel. This equates to about 700 receiving smallpox and 350 tularaemia vaccinations.

We have some parliamentary answers. Lord Gilbert, 1998, when asked about the smallpox vaccinations replied that a small number of troops had received smallpox but that he would not give an exact figure because of issues of National Security.

We have the accounts of the GWVs themselves. Under oath they are prepared to state that they received smallpox as part of a larger body of men and that these vaccinations were not recorded.

The MoD have continued to insist that only two smallpox vaccinations were given, one by private arrangements, and the other by mistake! They also insist that the extant, "Rabbit Fever", vaccination record is a forgery. These explanations are not satisfactory and in the case of smallpox somewhat contradictory.

WHAT DO WE KNOW?

It is unequivocally established from the records, from eye-witnesses, and by tacit admission of the MoD that the vaccines were administered very hurriedly and in breach of the normal protocols for vaccination. Some personnel received up to 10 different vaccinations on one day. The vaccination programme was experimental and given without any informed consent.

MoD memos expressing concern about this situation have recently been quoted in an exclusive article in the Big Issue although no such memos have been disclosed to the Independent Panel established to oversee MoD research programmes in this area.

The use of pertussis with anthrax involved the unlicensed use of pertussis as an adjuvant which was later shown not to provide any improvement in the level of antibody response. This was another experimental procedure, used without informed consent. It is of grave significance that an, admitted, MoD fax, which from mice studies indicated that pertussis with anthrax could have adverse health effects in humans, was not registered and is now lost. Furthermore, the whole experimental protocol for this study has also been lost.

The Unwin *et al* study concluded that the increased incidence of symptoms amongst UK GWVs was associated with the vaccines.

Despite all this evidence the MoD/GVIU/MAP continue to insist that the vaccines were given in accordance with normal practice and that there were no long term adverse effects from the vaccination programme (Professor Harry Lee in an address to the Independent Panel—29 March 1999).

It is clear from research in the states that the present anthrax vaccine is unproven as an effective treatment for soldiers exposed to aerosolised spores that would be inhaled. It is also apparent that only six out of 22 anthrax strains are effectively neutralised by the present vaccine, Nass 1999. Both anthrax and pertussis are known to induce autoimmune diseases, Nass 1999, 1998. The delays in producing a new vaccine and the continued use of a vaccine, now six years past its approved shelf-life, are unacceptable and requires much more detailed explanation and disclosure of the testing data.

I have become aware, through the press, of new vaccines prepared by Porton Down, against plague, Daily Express 99, again not disclosed to the Panel. A new smallpox vaccine grown on mammalian tissue has been announced in the USA, American Forces Press Service, 1999.

Even more disturbing is the Health and Safety Executive report filed by Porton Down, HSE, 1993, for the investigation of genetically modified organisms for vaccine manufacture. The organisms involved were—*E.coli* K12, *Vaccinia virus* (smallpox! and a carrier vector for gene-modified vaccines), *Francisella tularensis* (Rabbit Fever!), *Yersinia pestis* (plague), *Salmonella typhimurium, Bacillus subtilis, Bacillus brevis, Clostridium perfringens.* This information has not been disclosed to the Independent Panel.

All this supports the fears of the troops and the evidence of the records that experimental and untested vaccines could have been given to the UK and USA troops. It needs fully investigating.

THE ADJUVANT STORY

Adjuvants are administered to cause an enhanced immunogenic response to a vaccine which otherwise might not afford protection against the disease for which the vaccine is being used. Anthrax vaccine is well known to be of low immunogenicity. In the UK it was decided to use pertussis as an adjuvant. In the USA no adjuvant was officially given but recently there have been reports of the identification of squalene antibodies in the blood of USA GWVs who received their vaccines and were deployed to the Gulf and those who, although receiving the vaccines, were not finally deployed. Two UK GWVs were also found to be positive for these antibodies, Matsumoto, 1999, Rodriguez, 1999.

Squalene is a component of a widely used adjuvant, MF 59, which has been much used in animal studies involving experimental HIV vaccines. Its presence in GWVs indicates its use in undisclosed experimental vaccines or as an unapproved adjuvant for anthrax. Either way the troops have been used as experimental animals. Furthermore, the findings in UK troops requires explanation.

What American vaccines were given to UK troops?

How many American troops received UK vaccines?

What comparison of the effects of these vaccines has been made?

Again no discussion has taken place in the Independent Panel. Squalene is known to cause major adverse effects in humans when injected.

THE MYCOPLASMA STORY

Garth and Nancy Nicolson, 1996, 1997, 1998, in a series of peer reviewed papers, provide compelling evidence of the role of mycoplasmas, particularly *Mycoplasma fermentens incognitus,* in GWS/I. They have identified this organism in ~45 per cent of sick GWVs and developed an effective treatment, using powerful antibiotics doxycycline, ciprofloxacin, clarythromycin (but not penicillins) with suitable adjunct therapy. Initially the Nicolsons received ridicule and persecution (the story is well told by them in an article in "Criminal Politics", 1996). One extremely disturbing feature of their story is the possible identification of a gene-modified mycoplasma which might be part of an illicit or unknown BWs programme. A study of 1,000 GWVs using this regimen has just commenced in the USA.

The source of the mycoplasmas and other foreign viruses could be vaccines prepared using animal cells or tissues. These are well known and admitted in veterinary vaccines, Roth, 1998, Glickman, 1998.

No examination of UK veterans has been carried out and no treatment on these lines offered.

HUMAN ENDOGENOUS RETRO-VIRUSES (HERVS)

Howard Urnovitz in the States has explored this aspect of chronic disease. He has identified markers, RNA fragments, of multiple myeloma (a bone marrow cancer) in some GWVs along with a number of other unusual RNA fragments. These he sees as indicative of disturbance of the human genome as a result of exposure to toxic biological and/or chemical organisms and derivatives. Such disturbances could give rise to new chronic diseases which might be transmissible, Urnovitz, 1992, 1998.

TRANSMISSIBILTY

There are increasing reports of close family members of GWVs contracting similar GWS/I. This points to some infectious organism(s) which is/are transferred on prolonged and close contact Thomas, 1998; Fudenberg, 1999; Van Kleist, 1997; Nicholson, 1996.

THE CONSEQUENCES OF COMPRESSED MULTI-VACCINE ADMINISTRATION

It is important to recognise the variety of vaccines that were given to the GWVs. These included live vaccines containing attenuated organisms, polio, yellow fever, smallpox, oral typhoid (used in USA); whole dead organisms, cholera; plague; sub-cellular components of organisms, anthrax, tetanus, meningitis, pertussis, hepatitis B; immunoglobulins, hepititis A, botulinum anti-toxin.

When the knowledge of the vaccine regimens given to the troops became widely known an important paper appeared in the *British Medical Journal* by Graham Rook and Alimuddin Zumla. This argued that the vaccines administered would lead to a considerable shift in the immune response from a balanced distribution of Th1/Th2 cells to an unbalanced and dysfunctional increase in Th2 cells with a significant suppression of Th1 cells. The outcome of this change would be a shift from cell-mediated immunity to an excessive humoral response. There would be a reactivation of latent viruses such as Epstein-Barr virus, EBV, and herpes viruses, with an increased susceptibility to adventitious infections, and loss of important immune responses such as the control of viral infections and the destruction of cancer cells. The development of chronic autoimmune diseases would be facilitated. Organophosphates are known to promote similar immune responses.

This pattern of infectious illness is found in many GWVs. Nearly all have an active EBV infection. Many complain of their inability to deal with previously common place infections—"I catch everything that is going and it takes ages to shake things off". In the USA, GWVs showed an unexpectedly poor response to polio serotypes 2 and 3 not found in troops who had not been vaccinated according to the Gulf War regimens. This is indicative of a seriously compromised immune response to an effective and well-established vaccine, Urnovitz, 1998, Thomas, 1998.

Among the GWVs autoimmune diseases have appeared, Nass, 1999; multiple sclerosis-like illnesses, Sjorgren's syndrome, rheumatoid arthritis, ulcerative colitis, systemic lupus erythematosus. The latter is principally an autoimmune found in women but amongst GWVs it has a high prevelance in men. Lou Gehrig's disease (amyotrophic lateral sclerosis), also known as motor neurone diseases, is regarded, by some as an auto-immune disease, that affects the neuromuscular junction. It is much more common amongst GWVs than the normal population, Burton, 1997.

Some of the organisms in these vaccines, eg polio, measles, are known to populate and adversely stimulate the lymphoid tissue of the gut thereby damaging the integrity of the gut membranes in a manner that could extensively compromise gut function.

Others are known to affect neural tissue. Recently, in the USA, MRS (Magnetic Resonance Spectroscopy) has shown major defects in key brain areas, eg the brain stem, of some GWVs, Haley and Fleckenstein, 1999a.

We have no data on any of these aspects of immune disorders in UK veterans. No work has been done.

CONCLUSIONS

(1) Many procedures were experimental and did not obtain informed consent from the GWVs. This is both unacceptable and breaches medical ethics;

(2) Pertussis (Whooping cough) as an unproven adjuvant which had not been evaluated, and without the knowledge of one of the main suppliers;

(3) Anthrax vaccine was unproven against pneumonic infection and has shown to provide very limited protection;

(4) The immunological aspects of GWS/I have not been effectively addressed to date. Both diagnostic procedures and treatment possibilities remain unexplored;

(5) MRI, MRS, SPECT and PET scans should be taken of sick GWVs to look for evidence of brain damage;

(6) Data on rare conditions, Lou Gehrig's disease, nephrotic syndrome, systemic lupus erythematosus etc, associated with possible immunological damage should be compiled on a National Register.

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