

BACKGROUND TO THE USE OF
MEDICAL COUNTERMEASURES TO PROTECT BRITISH FORCES
DURING THE GULF WAR (OPERATION GRANBY)

INTRODUCTION

1. When Iraq invaded Kuwait in August 1990, a coalition was formed, initially to prevent any further Iraqi aggression and subsequently to liberate Kuwait itself. The nations involved in the coalition faced the possibility that Iraq might use weapons of mass destruction at its disposal against them. For Iraq, the attraction of such weapons was their potential to inflict massive casualties upon any forces opposing its regional ambitions.

2. Building upon the suite of protective measures already developed against chemical and biological weapons threats, the UK Government embarked on a programme to provide the best available means of protection for British troops against the specific and highly lethal agents which Iraq was believed to possess. In parallel with equipping our forces with detection and warning systems, together with individual and collective protection equipment, a range of medical countermeasures for use both before and after any attack was assessed, safety tested, acquired, deployed to the theatre of operations and, where appropriate, implemented in time for the campaign in early 1991. Achieving this in the wider context of preparations for war required an intensive and sustained effort by the staff of the Ministry of Defence and of other Government Departments and Agencies.

3. As a result of this work, British troops were provided with the best available defence against the threats which they faced. The fact that no Iraqi attacks using chemical and biological warfare agents are assessed to have taken place in no way detracts from the critical importance of ensuring that these protective measures were available at the time.

BACKGROUND

4. During the Gulf War a range of medical countermeasures were used, or available to be used, to protect British troops against Iraqi chemical and biological weapons (CBW). This paper sets out the background to these matters, including an explanation of the threat assessment at the time, the relevant scientific research upon which decisions were based, and more details of the specific medical countermeasures which were used or put in place.

Content

5. The paper consists of an initial general section which covers the CBW threat assessment and the overall response, including information that relates to more than one of the countermeasures, followed by more detailed sections on each of the individual medical countermeasures. The information in this paper has been derived from extant MOD records, supplemented by interviews with many of those involved with these matters at the time and documents supplied by other Government Departments and Agencies.

Related work

6. The MOD is in the process of establishing a research programme into the possible health effects of the combination of vaccines and tablets which were given to troops in the Gulf to protect them against the CBW threat. The results will both provide scientific data with which to address veterans' concerns and inform the Government's policy on the future use of such countermeasures. The Department is also funding two epidemiology studies which are looking into whether Gulf veterans are experiencing greater ill-health than service personnel who did not take part in the conflict, and into their reproductive health.

7. An MOD fact finding team is conducting a study into the way in which our vaccination programme was implemented in theatre, based on extant documentary evidence and supplemented by oral testimony. The results of this work will be made public once it has been completed.

8. Finally, the MOD is reviewing a number of specific events during the Gulf War in response to uncorroborated reports from British veterans that these may have involved exposure to chemical or biological weapons. The results of this work will be made public as each stage is completed.

CHEMICAL AND BIOLOGICAL WARFARE

The threat

MOD assessment

9. Following the invasion of Kuwait by Iraqi troops on 2 August 1990, the UK made assessments of the capabilities of the Iraqi forces in order to inform the UK's response to the developing crisis. From the outset, it was known that the Iraqi regime was seeking to acquire various weapons of mass destruction (WMD). The large number of casualties from chemical weapons (CW) during the Iran-Iraq war of the 1980s had already demonstrated that Iraq possessed this particular capability and was prepared to use it.

10. The initial UK assessment in August 1990 was that Iraq had a biological warfare (BW) capability which included the ability to use anthrax and botulinum toxin (BTx) in a variety of potential delivery systems. In November 1990 a revised assessment judged that Iraq had probably also developed plague as a BW agent.

11. These assessments were broadly shared by the US Government, although initially the US authorities did not share the UK assessment concerning plague.

12. The optimum delivery method for many BW agents is thought to be by aerosol, that is the production of a spray of fine liquid droplets or powder that will stay suspended in the air. Anthrax was assessed as most likely to be delivered in aerosol form and it was considered possible, but less likely, that it would be used to contaminate food and water supplies. Anthrax is generally not passed directly from one individual to another. BTx was also expected to be delivered by the aerosol route, although it was assessed as possible, but less likely, that it would be used to contaminate food and water supplies. Given the climatic conditions in the Middle East, BTx was assessed as unlikely to cause a secondary aerosolization hazard after an initial attack because it decays rapidly in high temperatures and sunlight; being a poison it does not spread by secondary transmission from one individual to another. By contrast, it was assessed that following an aerosol attack using plague as a BW agent, infected individuals would become a secondary source of natural contagion.

13. Iraq's CW capability was assessed as including nerve agents (also known as nerve gases), vesicants (also known as blister agents) and blood agents. The range of delivery methods believed to be available included mortar bombs, artillery shells, rockets and air dropped bombs. Ballistic missiles with chemical warheads were also assessed as probably available.

UNSCOM

14. In 1991, after the Gulf War had ended, the United Nations Special Commission (UNSCOM) began investigating Iraq's WMD programmes.

15. In terms of BW capability, Iraq has now told UNSCOM that it did possess munitions containing anthrax and botulinum toxin, but continues to deny any work on plague. This information was only obtained in 1995 after much initial denial and investigations into the Iraqi BW programmes continue.

16. UNSCOM has also established that the Iraqi regime had weaponised nerve agents including sarin (GB) and cyclosarin (GF). Both bulk material and filled munitions relating to these agents were found at the Iraqi facility at Muthanna in Autumn 1991.

The response

17. On the basis of its threat assessment, the UK was faced with the prospect that Iraq would use its CBW capabilities against troops taking part in Coalition operations; and that, if it did so, the lethal nature of these weapons would result in substantial British casualties. It was therefore the duty of the UK Government to consider both what CBW countermeasures were already available to British troops and to what extent it was necessary and possible for these to be augmented.

Protective measures

18. A range of CBW protective measures had already been developed for British forces, based upon the need to defend against the assessed capabilities of the then Soviet Union. These included: warning and detection systems; Individual Protection Equipment (IPE) - which consisted of specially-designed Nuclear, Biological and Chemical (NBC) suits with respirators to filter out harmful BW and CW materials; shelters designed for the collective protection (COLPRO) of groups of Service personnel; and individual medical countermeasures - that is those which improved the defences of the human body against a CBW attack - which are the subject of this paper.

19. Each of these protective measures provided protection in its own right and, when used with the others, contributed to a much higher level of overall protection. Thus the use of medical countermeasures was an integral and essential part of the protection strategy for British troops.

Medical countermeasures

20. Medical countermeasures fall into two categories. Prophylactic measures are used in advance, in the expectation of an attack. They usually take time to build up to their full protective effect. Post-attack measures are used where there are signs of poisoning or where infection is suspected, for their therapeutic value in respect of the particular agent which is believed to have been used.

21. The first line of protection is provided by the medical countermeasures which a Service person has already taken prophylactically and those post-attack therapies which are issued to each individual for immediate use. A wider range of post-attack therapies is available as part of the second line of medical arrangements to treat battle casualties.

BW medical countermeasures

Anti-BW immunisation

22. During Op GRANBY the MOD had a specifically targeted anti-BW immunisation programme in which three vaccines were used: anthrax and plague against the assessed threat of Iraqi BW agents, and pertussis as an adjuvant to anthrax. (Each of these is discussed in a separate section below.) The overall policy was that these vaccines should be administered on the basis of voluntary informed consent. The MOD is aware that many veterans regard this policy as having been breached in practice. A fact finding team has been established to look into the implementation of the vaccination programme* .

Other vaccines

23. In addition to the anti-BW vaccines, British Service personnel could also have received a number of other routine vaccinations at about the same time. These were those which Service personnel were normally required to have (yellow fever, tetanus, typhoid and poliomyelitis); those appropriate for travellers to the region (cholera); and those appropriate to particular categories of Service personnel (hepatitis B). Information on these six vaccines was made available by MOD in 1993.

24. Recent work on Gulf War records suggests that some troops also received meningitis vaccine, which was not listed in the 1993 memorandum. Some troops could also have received hepatitis A immunoglobulin, which was available in theatre. More information on the range of routine vaccinations received by different groups of service personnel will be sought as part of the current fact finding work* .

How vaccines work

25. A vaccine is composed of non-toxic and non-infectious material, which, when administered to humans or animals, induces an immune response which is able to prevent the development of a specific disease on subsequent exposures to the causative microorganism or toxin. Vaccines act in a number of ways: some induce the production of antibodies, whilst others induce mainly a cellular immune response. The active element of a vaccine might consist of live microorganisms which are unable to cause disease (attenuated microorganisms), killed microorganisms, modified forms of a toxin, or fragments of a microorganism or toxin (sub-unit vaccines). Different types of vaccine are appropriate for different diseases and circumstances.

26. In normal circumstances, vaccines offer a high level of protection and disease is rare in protected individuals (although cholera vaccine is known to provide only partial protection). In principle this protection can be overcome if the level of exposure to the agent causing the disease is sufficiently high, although in practice vaccine breakthrough is rarely if ever observed in public health situations. However, in the BW context, where very high doses can be delivered via the highly effective aerosol route, even successful immunisation does not guarantee complete protection.

27. Long-term side-effects associated with the use of vaccines are rare, while short term effects usually last between a few hours and a few days. The latter are often caused by collateral materials in the vaccine such as preservatives or other components of the vaccine which do not contribute directly to the immune response. The propensity for a given vaccine to produce such short term side effects is referred to as its reactogenicity.

Vaccine stocks

28. In 1990 MOD did not hold a stock of vaccines against the possible requirement to immunise against BW agents because vaccines are expensive and have a limited life. Hence there was an unavoidable time delay between the decisions to procure vaccines and the delivery of sufficient stock to initiate an immunisation programme.

Other BW medical countermeasures

29. British forces also had antitoxins and antibiotics available for use as post-attack therapy. (Each of these is discussed in a separate section below.)

CW medical countermeasures

30. During Op GRANBY, medical countermeasures against nerve agents were available in the form of Nerve Agent Pretreatment Set (NAPS) tablets, used prophylactically, and the autoinjectors known as Combopens, for complimentary post-attack therapy. Post-attack treatments were also available for vesicants and blood agents.

Licensing

31. A number of the medical countermeasures used during Op GRANBY were unlicensed in the UK at the time. In each case the decision to use an unlicensed product reflected the need to protect British troops against a specific threat in the absence of an appropriate UK licensed alternative.

32. The fact that a medical product is unlicensed does not mean that it is untested or is inherently unsafe. The licensing of medicines is a rigorous, time-

consuming and expensive process. Manufacturers of vaccines are only likely to apply for a UK licence if the potential market for the product warrants the efforts and costs involved. Licensing procedures cannot be accelerated: hence there was no possibility of obtaining a UK licence for any previously unlicensed product in the six months between the Iraqi invasion of Kuwait and the Coalition campaign to liberate it.

ANTHRAX

Properties as a weapon

33. Bacillus anthracis is a naturally occurring bacterium which has been found in a variety of environments, including soil, water and animal products. It is able to survive for prolonged periods in some environments by forming spores which are more resistant to desiccation, sunlight and extremes of temperature than the free living bacteria; this fact was recognised as long ago as the Second World War. The bacterium causes the disease called anthrax, which is usually contracted after the entry of spores to the body through cuts and abrasions (e.g. from contaminated soil). The mortality rate for this form of the disease (cutaneous anthrax) is between 5 and 20% in untreated cases. Occasionally the disease is contracted by inhalation of bacterial spores. This results in pulmonary anthrax which is extremely difficult to treat and is usually fatal.

34. The most likely mode of use as a BW agent would be by aerosol dispersion, which would lead to inhalation of the bacterial spores and hence to pulmonary anthrax. If inhaled into the lungs, anthrax spores pass to neighbouring lymph glands and germinate into vegetative bacterial cells. The bacteria then produce a toxin which causes death. After inhalation exposure, the initial symptoms of the disease are mild. Acute symptoms are seen within 48 hours. Without treatment or intervention, the mortality rate is likely to approach 100%. Antibiotics can be used successfully to treat pulmonary anthrax provided the nature of the infection is recognised early enough. However, there are generally no characteristic warning signs that such infection has occurred before prostration and collapse.

The response

35. The use of vaccine to provide protection against anthrax was already well established in 1990. A vaccine with a UK licence was available and the characteristics of that vaccine were well known and documented.

UK licensed vaccine

36. An anthrax vaccine has been produced by the Centre for Applied Microbiology and Research (CAMR) at Porton Down since 1956^{*T}. This vaccine has been licensed in the UK to the Secretary of State for Health as Medicines Control Agency (MCA) product licence number 1511/0037 since 1979. It is still being produced and is used primarily to protect veterinary and laboratory workers, and those employed in "hair and hide" industries, such as tanneries, woollen mills and bone-meal factories.

37. The active ingredient of the UK licensed human anthrax vaccine is the protective antigen (PA), which is produced by the bacteria when they are grown in a

culture. The PA is non-toxic and can be isolated from the culture fluid and purified to remove other materials. When used in a purified form in a vaccine, it can induce an immune response which provides protection against anthrax.

38. During the 1980s, work under MOD contract was carried out at CAMR to understand the protection against anthrax provided by PA-based vaccine. The essence of this work was published in the Salisbury Medical Bulletin*.

Live vaccine

39. Live spore vaccines are used for immunisation against anthrax of live stock globally and also for humans in China and former Soviet countries. The strains used have residual virulence which results in side effects and hence they are not considered suitable for human use in the West. Research had shown that the protection induced by a live spore vaccine was greater than for a PA-based vaccine against one of the more virulent (Ames) strains of anthrax. During Op GRANBY, the possibility of using a live anthrax vaccine was not pursued.

How to use the anthrax vaccine?

40. Once a programme of immunisation against anthrax was under consideration, attention within MOD focused on how its efficacy could be optimised and briefly on whether it should be given as a post attack therapy as opposed to being used prophylactically.

41. The option to use the anthrax vaccine as a post-attack therapy in conjunction with a course of antibiotics was considered because it was understood experiments using primates in the US had shown this to be effective. Although the UK intention was always to immunize in advance, it was recognised that there might be circumstances where a post-attack regime was the only option. In the event it was not necessary to explore the option of conserving anthrax vaccine supplies for post-attack use as sufficient were available for prophylactic immunisation.

42. Anthrax vaccine takes a significant time to elicit a protective response. The prescribed dosing schedule involves four doses of vaccine over a period of 32 weeks. Using this protracted immunisation schedule would have risked leaving British forces unprotected during Op GRANBY. There was therefore a requirement to devise ways of inducing immunity to anthrax more rapidly. With this aim in mind, possible adjuvants to boost the immune response to the anthrax vaccine were considered by MOD which ultimately decided to use pertussis vaccine for this purpose*.

Dose

43. For the Op GRANBY anti-BW immunisation programme, anthrax vaccine was to be given in an initial dose of 0.5ml, to be followed by the same dose three weeks and seven weeks later, in conjunction, on each occasion, with pertussis

vaccine as an adjuvant.

Procurement of anthrax vaccine

Source

44. The anthrax vaccine administered to British troops during the Gulf War was produced by CAMR and sold under a licence held by the Secretary of State for Health. At that time, this licensed anthrax vaccine was marketed and distributed commercially by Porton Products Limited. The vaccine was procured by MOD under this distribution and marketing agreement.

Testing

45. The National Institute for Biological Standards and Control (NIBSC) had been requested by the Department of Health (DoH) to assist with the evaluation and testing of the quality of specific batches of medical countermeasures as procured by MOD for use during the Gulf War.

46. All the batches of the anthrax vaccine intended for procurement by MOD - batch numbers 337 to 351 - were tested for compliance with specifications prior to release by NIBSC. CAMR itself also undertook routine testing of all batches, as required by the Product Licence, before material was sent to NIBSC. Some material examined at CAMR required re-testing, as provided for in the terms of the Product Licence. The results from one test on a single batch (348) did not meet the required criteria and this batch was withheld by CAMR. In the event, batches 337-347 and 349 were released from CAMR in 1990-91; batch 348 has never been released.

Datasheet

47. The DoH datasheet for the anthrax vaccine is at Annex A.

PERTUSSIS

48. Unlike the other two vaccines which were administered to British troops during the Gulf War as part of the anti-BW immunisation programme, the pertussis (whooping cough) vaccine was not used as a result of the threat assessment, but because MOD believed it offered a way of increasing the protection provided by the anthrax vaccine in the short time available between production of the vaccine and the expected commencement of hostilities.

49. Although use of the UK licensed vaccine was seen as offering the best available protection against anthrax, there was also considerable concern within MOD about whether it would be sufficiently effective against an aerosol challenge, or against particularly virulent strains, and about the time required for an adequate level of immunity to build up. The latter point was particularly important as the first dose of anthrax vaccine provided only minimal protection and it was not until the second, or possibly third, dose that significant immunity was developed. Hence the subsequent importance attached to the use of an adjuvant with the intention of providing adequate protection within the expected operational timescale.

Improving the effectiveness of the anthrax vaccine

Research

50. The main thrust of the work on anthrax vaccination carried out under MOD contract at CAMR from 1983 was to try to develop a vaccine that would provide optimal protection. Researchers at CAMR approached this problem by trying to understand the mode of action of anthrax vaccines by the addition of a number of different adjuvants, that is substances which might be used to boost the immune system to respond more vigorously to the simultaneous or concurrent use of a vaccine. This proved effective with a group of adjuvants which are known to stimulate a component of the immune system called the cellular immune response.

51. This was investigated further in a subsequent MOD sponsored project that was completed in 1989 by CAMR using a vaccine against whooping cough (Bordatella pertussis), which was produced at the time by Wellcome Research Laboratories. The published paper by Turnbull et al.* which was based upon this research, showed that the efficacy of the anthrax vaccine in giving wider protection against so-called vaccine resistant strains was enhanced when administered simultaneously with pertussis vaccine. The authors concluded that further tests would be needed to determine optimum dose sizes and schedules in relation to protection against challenge with a series of strains, various challenge sizes and challenge by the respiratory and oral routes.

52. On the basis of the extant research, in August 1990 it was suggested by

CBD Porton Down* that the use of pertussis as an adjuvant could significantly reduce the numbers and severity of casualties in the event of an anthrax-based BW attack. In considering this approach, it was noted that the expected beneficial effect was based upon limited animal experimentation and was unproven in humans; and that there would be an increased immunological challenge to service personnel as a result of using a further vaccine.

53. In the light of the operational circumstances, in particular the possibility of a BW attack occurring before full immunity had been built up based on the use of anthrax vaccine alone*, a recommendation from CBD in September 1990 to use pertussis as an adjuvant was accepted by MOD. The UK licensed anthrax vaccine was to be administered simultaneously with and in an adjacent site in deltoid muscle to the pertussis vaccine.

Dose

54. For the Op GRANBY anti-BW immunisation programme, pertussis vaccine was to be administered with the anthrax vaccine, in an initial dose of 0.5ml, to be followed by the same dose at three weeks and seven weeks later.

Declassification of information

55. In conjunction with the publication of this paper, the MOD is making available the results of a limited study relating to the use of anthrax and pertussis vaccines which was carried out at CBD Porton Down following the Gulf War. The study* concluded that the pertussis vaccine administered as an adjuvant to anthrax vaccine was ineffective in enhancing anthrax antibody levels, although it may have served to accelerate the early production of specific antibodies. This report, which was previously classified, was made available to the Medical Research Council and researchers into Gulf veterans' illnesses issues in December 1996.

Procurement of pertussis vaccine

Sources

56. In 1990 a UK licensed pertussis vaccine was produced by Wellcome Research Laboratories under product licence 0003/1538. The vaccine was not recommended for use in adults and the MCA has recently advised MOD that it was not licensed for this purpose. This licence is now held by Evans Medical Limited, but the vaccine is not currently in production.

57. There were, however, competing demands on this source, as there were already two preexisting orders: from the DoH for their infant vaccination programme and from Sweden for a similar programme. In order to honour both these orders it was assessed that MOD would be restricted to procuring 62,000 doses from Wellcome in late 1990 and therefore would have to procure another 40,000 from another supplier. (10,000 doses of the Wellcome vaccine were already available to

MOD. In the event a further 8,000 doses were made available, bringing the total to 80,000.)

58. A French manufacturer, Merieux, was identified who had sufficient stock available to supply a pertussis vaccine - which was not licensed in the UK, but was in France as Vaxicoq - for delivery in early 1991. In November 1990 MOD placed an order, through the Procurement Department of the DoH, for 40,000 doses of "Pertussis vaccine Adsorbed", 0.5 ml in pre-filled syringes supplied by Merieux under the trade name IMOVAX. This order was later increased to 50,000 doses.

59. At the recommendation of the DoH, NIBSC carried out toxicity tests on the imported vaccine and reported that the test results showed the batches to be within specifications.

Datasheet

60. The insert sheet which accompanied the Merieux vaccine is at Annex B1. A Wellcome datasheet for their pertussis vaccine is at Annex B2.

DoH anxieties about the simultaneous use of anthrax and pertussis vaccines

61. MOD had kept the DOH informed of its plans in respect of anthrax and plague vaccines, and had sought advice on ways of ensuring that products which were not licensed in the UK were properly tested before use. However, whilst both DoH and NIBSC were aware that MOD planned to use pertussis - DoH had been asked to acquire a stock from Merieux and NIBSC had been asked to test the vaccine - the fact that MOD planned to do so as an adjuvant was not disclosed or discussed with them.

The DoH fax

62. On 21 December 1990, a senior official in the DoH, having earlier telephoned the MOD division responsible for Op GRANBY policy matters - Secretariat (Overseas) (Commitments) (Sec(O)(C)) - sent a manuscript fax covering a letter from NIBSC which DoH had received earlier that day and which contained the results of animal tests involving anthrax and pertussis vaccines. At this time, this was the channel of communication between DoH and MOD on policy relating to medical countermeasures issues.

63. The DoH fax stated:

"We have previously discussed the anxieties my experts have about the simultaneous administration of anthrax and pertussis vaccine.

There are no such studies in humans that I am aware of, but you may wish to see the enclosed FAX which I have just received from [name omitted] of the National Institute for Biological Standards and Control which reports on animal

studies they have carried out.

I think you (sic) Medical department needs to be aware of these preliminary results".

The accompanying letter from NIBSC stated that:

"As you will know, we have recently carried out abnormal toxicity testing in laboratory animals on certain batches of B. anthracis and pertussis vaccine. When each of the two vaccines were tested alone they were not associated with an unusual degree of toxicity at single human dose level. However, when combined there was evidence of severe loss of condition and weight loss in animals.

I would emphasis that these findings are preliminary, but they do suggest that if used in man as a combined preparation, an enhanced degree of reactogenicity could occur. The users of these vaccines may wish to take these findings in consideration."

NIBSC had not been asked by MOD to undertake this work, but they had deduced that MOD was planning to use pertussis as an adjuvant and therefore decided that a check for interactions might be helpful.

Reconstructing what happened

64. The DoH fax was delivered to the addressee in MOD, who at some stage marked a file reference on it, but it was not logged in by the Sec(O)(C) registry until 31 December 1990. The original fax, which was ultimately placed on a Sec(O)(C) file, was not marked to anyone else for comment or information.

65. No copies of the fax have been found in a search of the surviving files from other divisions or organisations which might possibly have been involved. No reference to it has been found in other documents. In the extremely busy period leading up to the Gulf conflict itself, when those involved in dealing with this issue were in contact on a daily basis, it would not have been unusual for a matter of the sort raised by DoH to have been dealt with wholly orally. The authors of the NIBSC letter and the DoH fax, and the addressee of the latter, were therefore asked whether they had discussed the matter with others and if so with whom.

66. The NIBSC official believed he had discussed the matter with two, possibly, three MOD officials (not the recipient of the fax). The DoH official discussed it only with the MOD official to whom he had sent the fax. The MOD official identified three fellow members of staff, who were directly involved in dealing with related matters at the time, with whom the official believed the subject would have been discussed. All these individuals were contacted as part of a review of this matter which took place earlier this year. However, other than the addressee, no member of MOD's staff at the time has been found who now recalls discussing this matter or

seeing the fax in question.

67. There is no material on the Departmental record which shows whether the research findings of NIBSC or the anxieties of DoH were taken into account when formulating the policy on the use of pertussis vaccine, although the general issue of possible side effects was addressed in guidance concerning the anti-BW immunisation programme generally.

Scientific significance

68. In order to have been addressed properly, the contents of the fax would have had to have been considered by someone in MOD with appropriate scientific or medical knowledge. It cannot be demonstrated that this occurred. What then is the scientific significance of the NIBSC tests?

69. NIBSC and DoH were sufficiently concerned about the results of the tests to bring them urgently to the attention of MOD. However, this did not constitute advice that pertussis vaccine should not be used in this way. The information immediately available to MOD about the tests was limited and the advice of current MOD medical and scientific staff is that, had they received such a fax, they would have contacted NIBSC to obtain more information upon which to form a judgement.

70. It is not now possible to do this retrospectively: NIBSC advise that the data from the tests was not retained because of the sensitivity of MOD's immunisation programme, and therefore it is not available for reassessment. No other records of this matter beyond the letter and the fax have been found. NIBSC has recently advised MOD that as well as the tests on mice, there were also simultaneous tests on guinea pigs, which by contrast showed no obvious reaction. Their view is that on the basis of the 1990 results alone, it is impossible to draw any conclusions on possible long term side effects or to extrapolate the findings to the human situation.

71. Even taking the documents at face value does not help form a view of the significance that should have been attached to NIBSC's findings in 1990. There are well understood limitations on the interpretation of drug tests in lower mammals and it does not follow that a reaction seen in mice will necessarily be expected to occur in humans under the same conditions. Moreover, MOD has recently been advised that some loss of weight and condition in mice is to be expected in toxicity tests involving pertussis vaccine.

72. The Turnbull et al. paper* makes no reference to possible side effects. One of its authors has been contacted and could not recall side effects being identified in their research. The paper refers to the condition of the laboratory animals when recording that some showed signs of ageing, which were hair loss, anorexia and wasting in a proportion of the animals. MOD has been advised by CAMR that this effect was a result of the age of the animals and was not specific to those that received any of the vaccines.

73. The only way to determine whether the short term side effects observed in the mice in 1991 were significant, and in particular whether there are likely to have been any long term effects in humans from the use of anthrax and pertussis together, is to carry out appropriate research into these issues. This will now form part of the new MOD research programme into potential interactions between vaccines and NAPS, which was announced by the Minister of State for the Armed Forces on 14 July 1997.

PLAGUE

Properties as a weapon

74. Plague is caused by a bacterium, Yersinia pestis, and appears in two forms in humans: bubonic and pneumonic. Bubonic plague is transmitted by flea bite and, if untreated, has a fatality rate of about 50%. This was the disease which raged through Europe in the fourteenth century, killing about a third of the population, when it was known as the Black Death. Pneumonic plague is spread by aerosolised sputum and leads to an infection of the lungs due to inhalation of the organism. Untreated pneumonic plague is invariably fatal. If recognised and treated early, naturally occurring pneumonic plague will respond to antibiotics.

75. As a BW agent, Yersinia pestis is most likely to be delivered by the aerosol route and therefore to cause a pneumonic infection. The incubation period for pneumonic plague is typically 2-3 days. The disease then develops rapidly, overwhelming the body's natural defences. Pneumonic plague may be highly communicable under appropriate climatic conditions; overcrowding facilitates transmission. The initial presentation is of malaise, high fevers, chills, headache and aches and pains. Patients develop a cough with bloody sputum. The pneumonia progresses rapidly causing shortness of breath and the terminal event is a combination of respiratory failure and circulatory collapse.

The response

76. The assessment that Iraq possibly had plague as a BW agent was made in November 1990, at a time when discussion of the options available for countering the threat of anthrax and BTx were fairly well advanced. The possibility of vaccinating against plague was well established: there were two basic types of vaccine available in 1990: dead cell vaccine and live attenuated vaccine.

Dead vaccine

77. The main source of dead cell vaccine known to the UK in 1990 was Cutter Biological, an American firm which produced a plague vaccine which was regularly used by US troops on some overseas deployments. This vaccine is now produced by Greer Laboratories and is still in use by the US forces and by veterinarians, hospital diagnostic laboratory workers, researchers and in those who are visiting areas of the world where they might come into contact with the disease. A similar dead cell vaccine is manufactured in Australia by the Commonwealth Serum Laboratories and is marketed for use in Australia and Asia.

78. A dead cell vaccine is produced by growing a culture of the fully virulent organism, purifying it and then killing it with formaldehyde. Side effects, like the

immune response itself, are caused by the human body recognising foreign proteins and reacting to them. However, as the organism has been killed, some of these proteins are no longer the same as would be found in live plague organisms, and consequently the efficacy of the vaccine is limited.

79. In December 1990, as part of the process of developing options for combating the threat of plague, CBD assessed that it could, theoretically, produce a dead vaccine of a similar nature to the Cutter vaccine. This idea was not pursued further.

Efficacy

80. In considering the use of the dead cell plague vaccine, concerns were raised about its efficacy. At the time of Op GRANBY, there was no data on the protection it afforded against pneumonic plague. It also had a reputation for reactogenicity. Nevertheless, on the basis of the available data, the dead cell vaccine offered the best option for protecting British troops from plague. It is still routinely used at CAMR and CBD as part of the standard protection for staff working with *Yersinia pestis*.

81. The possibility of using an adjuvant with plague was considered, but not pursued. The likelihood of a general adjuvant effect occurring from the stimulation of the immune system by administration at the same time as the anthrax and pertussis immunisations was also considered, as well as the balancing potential for interference between the vaccines. The policy adopted was for plague vaccine to be administered concurrently with the second anthrax and pertussis doses to take advantage of the adjuvant effect.

Live vaccine

82. Live attenuated vaccines* against plague are more effective in combating the disease, but they also carry a higher risk of serious side effects. Such vaccines were produced by a number of laboratories throughout the world, including those in what was then the Soviet Union, but not recommended for use in the West because of doubts about purity and safety, with a range of possible known side effects including liver abscesses.

83. The option to produce a live vaccine at CBD was pursued during Op GRANBY. It was assessed that, in an emergency, CBD could produce enough live vaccine to immunise the UK's troops within six weeks, although such a vaccine would be unlicensed. By late February 1991, CBD had produced, as a contingency measure, enough EV76 strain plague to manufacture 40,000 doses of live vaccine. However, this next step was never taken and the plague cultures were subsequently destroyed.

Dose

84. For the Op GRANBY anti-BW immunisation programme, plague vaccine was to be given in an initial dose of 1.0 ml followed by a further 0.2 ml dose after four weeks.

Procurement of plague vaccine

Sources

85. Initial assessment identified a number of possible sources for plague vaccine around the world which potentially offered a range of vaccines: both killed and live. However, there was, and is, no UK manufacturer of plague vaccine of either kind. The UK's initial, and ultimately only, enquiry was to seek a stock of the vaccine known to be used by the US DoD.

Cutter vaccine

86. The plague vaccine produced by Cutter Biological, part of the Miles group, was licensed by the US Food and Drug Administration (FDA). Cutter Biological's licence number was No. 8 in the US and No. 24 in Canada. (In the US licence numbers refer to the firm producing the drug rather than to the licensed drugs themselves.)

87. In 1990 the US DoD held a large stock of the Cutter plague vaccine. By agreement, the MOD made a priority acquisition of 4,000 20ml bottles of Cutter Vaccine USP from DoD in January 1991. This was the only stock of plague vaccine procured by MoD during Op GRANBY.

88. The available shipping data is not precise, but the US DoD has confirmed that 4,000 vials of plague vaccine were transferred from the US Mechanicsburg Army Depot, Pennsylvania to the UK. The batch numbers involved are not recorded. The shipment of 4,000 vials was escorted by a British Service officer by air from Washington to London on 16 January 1991.

Testing

89. The Cutter plague vaccine was not licensed in the UK. However, US Food and Drug Administration (FDA) Release Letters were available for lot numbers 10G05, 10H02 and 10H03.

90. Samples from these three batches of plague vaccine had been obtained in advance for testing by NIBSC, who advised that they complied with quality specifications.

Datasheet

91. The Cutter product safety leaflet for the plague vaccine is attached at Annex C.

BOTULINUM TOXIN

Properties as a weapon

92. Botulism is a fatal form of poisoning. In its natural form it occurs as the result of eating food which the Clostridium botulinum bacterium has contaminated by producing BTx. This contamination usually arises as a result of poor canning techniques.

93. There are eight types of botulinum toxin (BTx A, B, C1&2, D, E, F & G) which differ with respect to their structure, toxicity and immunogenicity. Most naturally occurring outbreaks of botulism in humans are caused by types A, B and E, with smaller numbers caused by types F and G. In 1990 it was assessed that Iraq had weaponised types A, B, E and possibly F. BTx is several orders of magnitude more toxic than the chemical warfare agents cyanide and sarin.

94. The resulting illness is characterised by clinical manifestations relating primarily to the nervous system. Visual difficulties (blurred or double vision), difficulties in swallowing and a dry mouth are the first signs. Vomiting, constipation and diarrhoea may be present. Neurologic symptoms usually appear within 12-36 hours, sometimes several days, after eating contaminated food. It kills by attacking the nervous system generally and causing paralysis. Cases are treated by hospitalisation and artificial respiration. In general the shorter the incubation period, the more severe the disease and the higher the fatality rate.

95. Inhalation of BTx, the optimum and expected BW agent delivery route, would lead to the development of symptoms after 6-12 hours, with death from asphyxia as a result of respiratory muscle paralysis following 24 hours later.

The response

96. In order to provide protection against an attack using BTx, consideration was given to both prophylactic and post-attack countermeasures.

Vaccine

97. In August 1990 active immunisation was considered by CBD to be the most appropriate medical countermeasure to deal with the threat of BTx. However, the MOD did not have any BTx vaccine in stock and, whilst available in principle, in practice it could not be acquired in time.

98. The Michigan Department of Public Health in the US produced an unlicensed vaccine which offered protection against BTx types A-E. This had been in use for at least twenty years. At the time of Op GRANBY, CAMR was producing an

unlicensed vaccine against BTx type F for the US DoD. It was assessed that CAMR was capable of producing a vaccine to protect against BTx types A, B, E and F at the time of Op GRANBY*, but it was heavily engaged already in producing anthrax vaccine for MOD. None of these potential suppliers could make vaccine available to MOD in the necessary timescale*. An MOD assessment in August 1990 concluded that a CAMR vaccine for BTx types A-E & F would not be available for nine months.

Anti-toxin

99. A post-attack therapy for BTx can be produced in the form of anti-toxin, which provides individuals suffering from BTx poisoning with antibodies harvested from either humans or animals which had already built up the appropriate immunity. Initially the manufacture of a BTx antitoxin by MOD during Op GRANBY was seen as an interim measure until BTx vaccine became available.

100. In order to create an anti-toxin, blood plasma is extracted from human volunteers, or animals, that have previously been vaccinated with a toxoid - an inactivated toxin capable of eliciting immunity without killing the host as would a normal toxin*. The plasma is then fractionated so that the immunoglobulin (ie antibodies) created by the vaccination can be mixed with other, neutral immunoglobulin. Potentially the resulting antitoxin could be used prophylactically or as a post-attack therapy.

101. Various animals could have been used to produce animal-derived serum, including horses and goats. For both these animals, the resulting serum is reactogenic, with the risk of an adverse reaction if used in humans. However, equine serum was regarded as much more reactogenic than goat serum.

102. In the event UK programmes to produce both human- and goat- derived serum were undertaken. The possibility of producing an anti-toxin from horses was also briefly considered, but not pursued.

Limitations

103. There are certain inherent difficulties with the use of antitoxins as a form of protection. First, antitoxins inevitably contain proteins from the source - other humans or animals - which can cause a serious adverse reaction when injected. The more "foreign" the protein, the more severe the reaction: hence animal-derived antitoxin carries more risk than human-derived material. Moreover, repeated use of antitoxin carries a greater risk of reaction, because the human body is likely to have built up antibodies to foreign proteins after the first dose and is likely to reject a second dose more vigorously than the first.

104. Second, antibodies from antitoxin are only likely to remain in the body for a very limited period. For example, in 1990 a licensed antitoxin for hepatitis A, Normal Human Immunoglobulin, was available, but was judged to be effective for only three months. Assessments of the effectiveness of a BTx antitoxin suggested

that this might be as short as a week.

When to use the antitoxins?

105. On the basis of test results from NIBSC, the likely short term effectiveness of the antitoxins and the risk of a reaction to repeated doses, it was agreed that the goat antitoxin would not be used prophylactically and, on account of the limited amount of human antitoxin available, it was decided that this would also be retained for use therapeutically.

106. The decision to use either of the antitoxins in the field would have been based upon the real and immediate threat to life posed by exposure to BTx.

Dose

107. The two BTx antitoxins were available in 2ml vials. The dosage used would have depended upon exposure: the goat antitoxin neutralised '5 lethal human doses' of BTx types A, B, E & F, whilst the more potent human antitoxin neutralised '10 lethal human doses' of BTx types A, B, C, D & E.

Procurement of BTx antitoxin

Sources

108. At the time of Op GRANBY, two Botulinum antitoxins were licensed in the UK by the MCA to the DoH. One licence had been granted in 1987 and the antitoxin was produced by Connaught Laboratories Ltd in Canada. The DoH had in 1990, and still maintains, a small stock of this vaccine to deploy in the event of a naturally occurring outbreak of botulism. There is no record of MOD seeking to acquire antitoxin from this source: possible reasons include the fact that it was a horse-derived serum and that it only provided protection against BTx types A, B & E.

109. The other licensed source was the Lister Institute, to which a UK product licence had been granted in 1973, but this institute had subsequently closed down and the licence had not been taken up by anyone else.

Producing serum

110. A programme was established at CBD in October 1990 to produce 3,000 doses of human serum, based on plasma from volunteers who had previously been immunised against BTx in the course of their work at CAMR and CBD. This human antitoxin would only provide protection against BTx types A-E because those donating plasma had only been immunised against those types. Also, since the programme depended upon a restricted number of suitably immunised volunteers, there was an inherent limit to the amount of anti-toxin which could be produced in this way.

111. A separate programme at CBD to produce 17,000 doses of animal-derived serum was also begun in October 1990, to provide protection against BTx types A, B, E & F.

112. Subsequently MOD acquired some 4,500 doses of human antitoxin and some 24,000 doses of goat antitoxin, of which 3,000 and 17,000 respectively were pre-positioned in the Gulf. Ultimately a further 26,000 doses of goat antitoxin were available.

Testing

113. The two antitoxins available during Op GRANBY were produced at the time to meet a specific threat and were consequently unlicensed.

114. NIBSC tested both antitoxins and advised that they were both of satisfactory quality for therapeutic use.

Datasheets

115. Draft datasheets for the two BTx antitoxins are at Annexes D and E.

BIOLOGICAL ANTIBIOTIC TREATMENT SET

116. In parallel to the prophylactic measures aimed at combating anthrax and plague, steps were also taken to provide a supplementary post-attack treatment which would provide further protection to support the protective effects of the two vaccines. This Biological Antibiotic Treatment Set (BATS) consisted of a powerful antibiotic (doxycycline) procured as self-administered capsules, which were to be held by individuals and taken on the orders of local commanders.

117. It was originally envisaged that BATS would be used in the event of an BW attack involving anthrax. When the threat assessment for plague was made, it was considered that BATS would also be applicable as a post-attack measure for this as well. However, BATS was not intended for use in the event of any BTx attack: BTx is a toxin, not a bacterial agent, and hence antibiotics are not an appropriate treatment.

118. The choice of which antibiotic to use in BATS was based on a number of considerations, including tests to determine the antibiotic sensitivity of probable bacterial agents, the results of US studies into the treatment of anthrax, and potential side effects.

119. The likely benefits of the use of an antibiotic in this way were assessed as providing some, unquantified protection in the event of exposure to anthrax or to plague. This was always envisaged as being an initial measure, to be supported by other treatment when a battle casualty received further medical aid.

120. In addition to BATS, a further antibiotic, Ciprofloxacin, was also specifically procured and held by medical staff as a post-attack therapy.

Dose

121. BATS consisted of 10 doxycycline 100mg capsules to be taken twice daily for 5 days.

MEDICAL COUNTERMEASURES AGAINST NERVE AGENTS

Properties as a weapon

122. Nerve agents comprise a family of highly toxic organophosphorus compounds several of which have been developed by a number of nations for use as a weapon of war. Their physical properties cover a range between volatile liquids such as sarin (GB), which are of a similar consistency to petrol and where the primary risks arises from inhalation of the vapour, and those which have relatively low volatility such as VX, which approximates to engine oil and where the risk is greatest from contact with skin.

123. A nerve agent acts by binding to the enzyme acetylcholinesterase (AChE), which is present throughout the human body and is critical to the transmission of impulses (signals) between nerves, and from nerves to muscles, glands and other organs. When a nerve agent enters the body by inhalation or contact, it binds to the available AChE and prevents that enzyme performing its normal function. This is known as cholinesterase inhibition and leads to over-stimulation of the nervous system, giving rise to the characteristic symptoms of nerve agent poisoning.

124. These symptoms progress from a feeling of general malaise, pinpoint pupils (miosis) and dimmed vision, excessive sweating, salivation and runny nose, breathing difficulties, through nausea and vomiting, muscle tremor, involuntary urination and defecation, to loss of consciousness, convulsions and death from respiratory failure. The speed of onset of these signs and the rate of increase in severity depend upon the dose and route of entry into the body. The most rapid route is by inhalation, 1-5 minutes, and the slowest is after absorption through the skin, 30-60 minutes.

125. Sub-lethal doses of nerve agent still require hospitalisation. If not treated, severely poisoned casualties will require critical care and may have long term damage. Less severe cases, for example those exhibiting the characteristic eye symptoms, may also suffer the effects for some weeks thereafter.

THE RESPONSE

126. The primary defence for British troops against nerve agent poisoning during the Gulf War was specialised protective clothing worn with a respirator, called Individual Protection Equipment (IPE). However, IPE can be breached or it may not be being worn at the moment of attack. Hence, given the very rapid onset of nerve agent poisoning and its lethality, additional protection was also provided.

Pretreatment against nerve agents

127. British troops were given a pretreatment regime of Nerve Agent

Pretreatment Sets (NAPS) tablets: one tablet containing 30mg of pyridostigmine bromide to be taken orally every eight hours. A week's supply - 21 tablets - was sealed in a single packet. The tablets were to be self-administered on command.

128. Pretreatment with the carbamate pyridostigmine bromide mimics the action of a nerve agent in that it binds to AChE, but unlike nerve agent it does so temporarily and the dose of pyridostigmine bromide is calculated to bind only a proportion of the AChE. Hence, only the remaining free AChE is available to be bound by nerve agent in any subsequent attack. Since any nerve agent which does not bind to AChE is rapidly broken down, within minutes, this allows the proportion of AChE which has been protected by the pyridostigmine bromide to regenerate spontaneously, thus ensuring the nervous system will continue to function.

129. Pyridostigmine bromide has been successfully used since 1955 to treat men and women suffering from the neuromuscular disease myasthenia gravis. The dose of pyridostigmine bromide given to myasthenia gravis patients ranges from 360mg to 6000mg daily, sometimes for many years. With the introduction of drug licencing in the UK in 1972, a treatment using pyridostigmine bromide in this way was granted a product licence of right and a full product licence was subsequently awarded in 1986.

Post-poisoning therapy

130. Post-poisoning therapy requires the administration of a combination of three drugs: Atropine, P2S and Avizafone. This is carried out at the first appearance of signs of poisoning by intramuscular injection into the thigh using an automatic self-injection device known as a Combopen, usually through protective clothing. If signs or symptoms persist, then a second dose is injected 15 minutes later and if they continue a third, 15 minutes after that. Each Service person was issued with three Combopens for self or buddy aid.

131. Atropine blocks some of the effects of nerve agent poisoning; hence it is important to provide atropine as quickly as possible to casualties. P2S (pralidoxime mesylate) is an oxime which reactivates AChE which has been rendered inactive by nerve agent. Avizafone is a water soluble pro-drug which is rapidly converted to diazepam (valium) in the body and is included for its anti-convulsant and muscle relaxing properties.

History

132. The UK Nerve Agent Pretreatment Set (NAPS) L1A1 was accepted into service in 1981 because the then existing combination of pretreatment and post-poisoning therapy did not protect effectively against all nerve agents. In particular, it did not protect against soman (GD), which inhibits AChE in a manner very similar to the other nerve agents, but rapidly changes its character ("ages") to become totally resistant to therapy by oxime (P2S). Pretreatment with NAPS overcomes this problem.

133. Pyridostigmine bromide was selected as the active element because it remained effective for a prolonged period (8 hours); it was listed in the British Pharmacopoeia as an existing drug with a long history of clinical use and safety; and it was thought incapable of crossing the blood-brain barrier and was thus unlikely to affect the performance of Service personnel. Pyridostigmine bromide provided protection within 2-3 hours after the first tablet was taken and maximum protection after the first 48 hours of taking the tablets. Overall, it gave significantly increased protection against all nerve agents when used in combination with post-exposure therapy.

134. Pretreatment tablets based on pyridostigmine bromide were, and are, in use with the US Armed Forces and other NATO allies, with whom British forces generally expect to operate alongside.

Trials

135. Human trials looking at the safety of using pyridostigmine bromide in unpoisoned soldiers were conducted at CBD Porton Down from 1972. The dose of pyridostigmine bromide was based upon animal studies and aimed to achieve an inhibition of blood AChE which was known to protect against nerve agent poisoning (30% inhibition). Extensive studies were made of the effects of pyridostigmine bromide given as 30mg tablets every 8 hours over a period up to 4 weeks.

136. Studies over a period of 14 days showed no clinically significant effects upon heart rate (resting or exercise), blood pressure, respiratory function, pupil area, behaviour or car driving. Some subjects reported mild side effects such as gastrointestinal disturbances (e.g. diarrhoea), which were not clinically serious and would not interfere with military duties.

137. Some studies were conducted on soldiers carrying out their normal activities and in those working in a hot environment. In the former case the dosage regime was well tolerated with few side effects. In the latter case pretreatment of military personnel working throughout a day time temperature of 35°C and a night time temperature of 22°C with a relative humidity of 43-52% (analogous to the Gulf conditions) showed only a slight decrease of 6-7 heartbeats per minute in pre- and post-exercise measurements.

138. Studies in men exposed to a low concentration of sarin vapour demonstrated that the effects of pyridostigmine bromide and sarin were not additive. Although pyridostigmine bromide did not reduce the miotic (pupil contracting) effects of sarin, the recovery time was improved and the aversion to light was reduced.

139. No adverse effects upon liver and kidney function were determined in these trials. The maximum period for which an individual took NAPS during these trials was 28 days.

140. Fertility studies were also carried out in animals which concluded that NAPS would be safe for use in men and women of child bearing age.

Consideration of the use of NAPS during Op GRANBY

141. In August 1990 CBD were requested to consider any possible adverse reaction between the taking of NAPS, the administration of Combopens, with the other prophylaxis being administered to Op GRANBY personnel (ie various routine vaccinations and anti-malarial tablets). Based on the information available at that time, CBD advised that no significant adverse reactions should be expected.

142. The possible effect of the conditions in the Middle East on the action of NAPS was also considered, particularly the possibility that this might increase the level of AChE inhibition. This was judged to be unlikely unless severe dehydration (and heat stress) had occurred.

Procurement of NAPS and Combopens

143. The initial UK supply of NAPS was manufactured in 1982-3 by Roche Products Ltd, who also made another product based on pyridostigmine bromide, Mestinon 60mg, used in the treatment of myasthaenia gravis. This purchase of NAPS had a nominal shelf life of five years, so a further purchase was made in 1988 from Duphar BV, following competitive tender. MoD took delivery in 1989 and this new stock of NAPS was distributed to units the same year.

144. Although MoD had large stocks available during the Gulf War in 1990-91, NAPS was also being taken by British troops in theatre and therefore these supplies were being used up. Hence further procurement was considered and in the event additional supplies were ordered from Duphar BV which were delivered in March 1991, after the hostilities had ended.

145. In October 1990, CBD analysed samples of nominally life-expired NAPS which had been produced in 1982 by Roche Products Ltd. Tests showed that the pyridostigmine bromide content of the tablets remained within the acceptable range. If necessary, therefore, the life-expired stocks of NAPS could still have been used as an emergency supply.

146. The latest model of Combopen, L4A1, was procured from Duphar BV in August 1989.

Licensing

147. Work by MOD to obtain a Medicines Act product licence for NAPS began in July 1980. However, a series of delays, including the change of supplier - at which point it was made a contractual term that the supplier would obtain a product licence - meant that it was not until August 1993 that this was completed. NAPS is licensed by the Medicines Controls Agency to the MOD for the pretreatment of service personnel

at risk from poisoning by organophosphorus cholinesterase inhibitors, under product licence 04537/0003 which expires in 1998.

148. Combopens were licensed in June 1996 under product licence 04537/0004.

Datasheet

149. The current datasheet for NAPS is at Annex F. The datasheet for the Combopen is at Annex G.

Ministry of Defence
Whitehall
London

October 1997

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- * See paragraph 7 above.
 - * See paragraph 7 above.
 - * In 1990 CAMR was part of the Public Health Laboratory Service (PHLS) which was a non-Departmental public body responsible to the Department of Health.
 - * Turnbull et al. "Protection conferred by microbiologically-supplemented UK and purified PA vaccines", Proceedings of the international workshop on anthrax, Winchester, April 11-13 1989: pp89-91. Broster et al. "Protective efficacy of anthrax vaccines against aerosol challenge", *ibid*: pp91-92. Salisbury Medical Bulletin, Special Supplement, No.68.
 - * See paragraphs 47-71 below.
 - * Turnbull et al. "Protection conferred by microbiologically-supplemented UK and purified
 - *
What is now the Chemical and Biological Defence (CBD) sector of the Defence Evaluation and Research Agency (DERA), situated at Porton Down, was known as the Chemical and Defence Establishment (CDE) between 1970-1991 and as the Chemical and Biological Defence Establishment (CBDE) between 1991-1996.
 - * It was assessed that the level of protection reached a peak after the fourth and final dose of anthrax vaccine at 32 weeks, see paragraph 42 above.
 - * "Operation GRANBY: The effect of co-administration of the Pertussis vaccine on specific antibody titre development to the anthrax vaccine in man." February 1992.
 - * See paragraph 38 above.
 - * These are produced from a culture of attenuated live vaccine, EV76, which differs from virulent plague in that it can be overwhelmed more easily by the human immune system.
 - * BTx type F is serologically unique and therefore requires a specific antibody.
 - * In 1990 CAMR also produced, and licensed to Porton Products Ltd, a therapeutic form of BTx called Dysport Injection 500U/Vial, which was licensed as an therapeutic injection for sufferers of Blepharospasm, a form of Dystonia. This is not a treatment for BTx poisoning.
 - * Hence a toxoid is analogous to the main component of a dead cell vaccine. No anti-toxin

13 1

equivalent to a live vaccine exists, because BTx is a chemical compound, not a living organism.