

Part VII. Human studies with treatments

Overview

Human studies to develop treatments were conducted throughout the period covered by the survey. The largest programme of work (which continues today) sought to develop treatments for systemic nerve agent poisoning. Two forms of treatment were explored in human studies: prophylactics, which guard against the effects of poisoning, and therapies, which treat the effects. Prophylactics were developed as tablets and, in practice, are usually taken on a regular basis whenever the threat of nerve agents being used against the Armed Forces is felt to exist. For example, Service personnel serving in the Gulf War started taking prophylactic tablets before they arrived in theatre and continued to take them while they were there. Therapies, taken after exposure to nerve agents, were developed as either injections or tablets.

The forms of treatment developed for nerve agent poisoning in human studies at Porton fall into distinct categories.

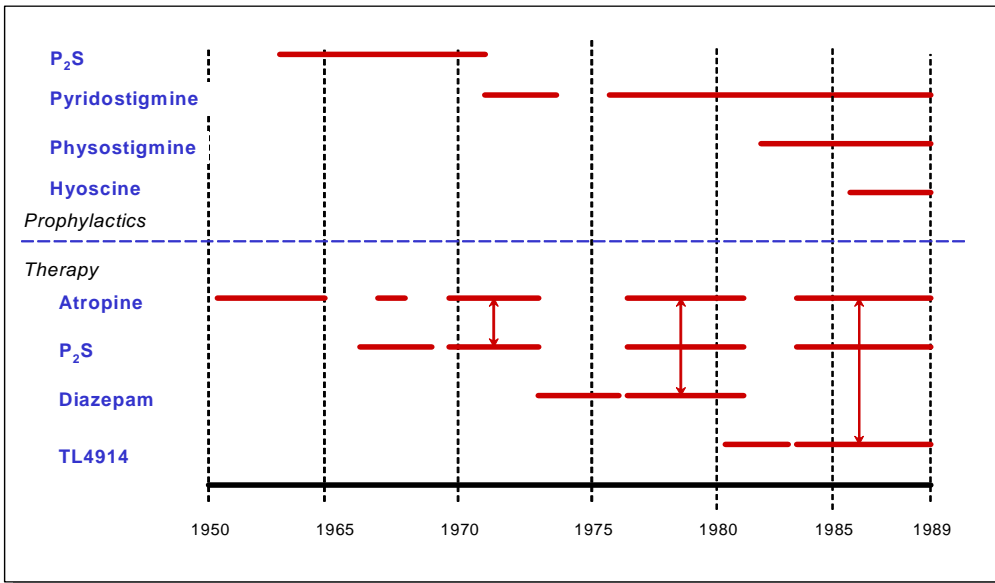
- Therapies which treat the effects induced by nerve agents Atropine sulphate falls into this category, as does diazepam (and a soluble form of it, TL4914) which alleviates the tremors and convulsions induced by severe nerve agent poisoning.
- Therapies which reactivated ChE inhibited by nerve agents P₂S¹ is an example of this type of therapy.
- Prophylactics which are reversible inhibitors of ChE These treatments protect ChE from attack by nerve agents. Pyridostigmine bromide and physostigmine salicylate are examples of this category.

Chapter 19 describes the human studies conducted to develop treatments for nerve agent poisoning. These studies include evaluations of effective dose levels, the effect of the treatments on physiology and performance, and ways in which the treatments are administered. Therapies were studied in combination as well as individually. The first figure below shows the human studies with nerve agent treatments. The therapies studied in combination are connected by red arrows. Prophylactics were also studied alone and in combination with therapies, but the figure would become too cluttered if these combinations were shown. Instead they are explained in the text of Chapter 19.

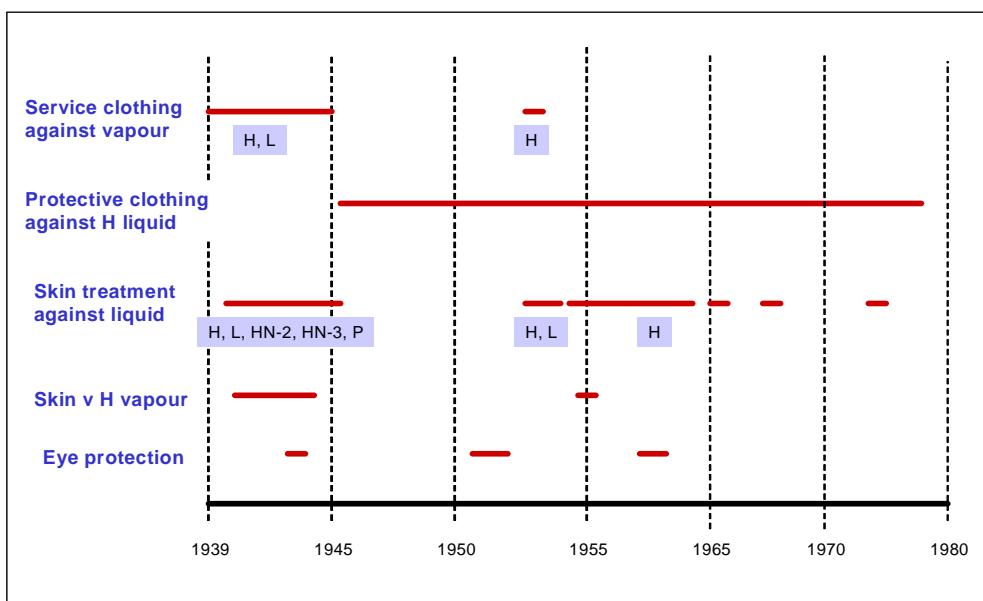
Treatment work during World War II was devoted to protecting the skin against the "traditional" war gases. Various forms of treatment were considered: impregnating normal Service clothing with powder or charcoal to protect the skin from H and L vapour; ointments and creams to decontaminate the skin from liquid H, L and nitrogen mustards (HN-1, HN-2, HN-3); ointments to protect the skin from vapour effects; and methods of treating H blisters. Methods of decontaminating clothing, equipment and food were assessed. Studies explored whether protective clothing prevented the passage of vesicants in liquid form (sometimes referred to as "penetration studies").

Some of these studies continued after World War II. In particular, many penetration studies were conducted to test a wide range of fabrics although post-war work considered only H liquid. World War II work on skin decontamination and treatment was extended in attempts to find one procedure which was effective against all forms of liquid agent, notably H, G and V. Human studies were confined to H; G and V work being conducted with animals or in the laboratory. Various eye treatments were considered. Chapter 20 describes human studies relating to skin protection. The second figure below depicts an overview of human studies investigating treatments.

¹ In the terminology of 1958, the full name of P₂S was "2-hydroxyiminomethyl-N-methylpyridinium methanesulphonate". Later in 1971 terminology had changed and the name "pralidoxime mesylate" was used.



Human studies with nerve agent treatments



Human studies of skin protection

Chapter 19. Treatments for nerve agent poisoning

19.1 Atropine² studies: 1947 - 1968

19.1.1 Introduction

Atropine blocks the action of acetyl choline (ACh), the chemical which transmits messages between nerve cells and muscles. Nerve agents inhibit ChE, whose normal function is to destroy ACh, thus leading to over-stimulation of the nervous system. By reducing the action of ACh, atropine prevents this over-stimulation. Atropine relieves bronchial spasms and helps dry up bodily secretions such as saliva and mucus. During World War II Porton explored, in animal studies, whether atropine would relieve the salivation prominent after poisoning with H [1, 2]. It was found to have little therapeutic effect but the properties of atropine naturally led it to be considered as a treatment for nerve agent poisoning [3].

Animal work in 1947 suggested atropine was of considerable value as therapy in cases of nerve agent poisoning [4] but there was some debate over the dose that ought to be recommended for man. By 1950, based on animal studies, Porton recommended a therapeutic dose of around 2.5 mg, while the US was using around 2 mg [5]. Doses corresponding to 2 mg per man and 3 mg per man were studied in animal work at Porton in 1951 and 1952 [6]. Either dose was found to save significant numbers of animals given lethal doses of GB but only if administered within 2 minutes of intoxication. A second dose of 2 mg (total dose of 4 mg) further improved chances of survival but only if given "well within 10 minutes" of intoxication [6].

The speed with which atropine needed to be given after nerve gas poisoning meant that Service personnel would have to carry atropine with them and administer the dose themselves. Military commanders were worried about the effect on military efficiency of indiscriminate self-administration [7]: after all, soldiers may not reliably be able to recognise they had been exposed to nerve gas and might, therefore, give themselves atropine unnecessarily. Thus, human studies at Porton examined the effect of atropine in the absence of nerve agent poisoning. These studies sought to find a dose of atropine which was effective against nerve agent poisoning but would not in itself incapacitate. Other studies examined ways in which Service personnel could administer atropine to themselves.

19.1.2. Effect of atropine and recommended doses

The first human study was carried out in 1952. At that time atropine was used as a medicine but the maximum clinical dose was 1 mg [8]. The effects on man of the higher doses recommended for nerve agent therapy had not been explored systematically. US work suggested that doses up to 3 mg produced dryness of the mouth and throat, dizziness, tiredness, changes in vision and increased heart-rate [8].

Various measurements were taken of volunteers' physiology before and after atropine was given, including pupil size and response to light, near and visual acuity, intra-ocular tension, resting pulse rate, blood pressure, ECG, breathing capacities, blood sugar levels and blood analysis. The study included exercise, in which men stepped onto and off a stool the height of which was set to establish a particular work rate. The volunteers exercised on two successive days with atropine being given before the exercise on the second day.

Atropine was given by IM injection: 44 men received 2 mg; 12 received 3 mg and 45 received 5 mg. Some of the volunteers fasted. The observations made included:

- all men complained of a dryness of the throat and mouth, usually slight after 2 mg but for some of the men who received a dose of 5 mg severe enough to make swallowing dry solid food difficult;

² "Atropine" is used as a shorthand for atropine sulphate throughout.

- the men who had a 5 mg dose were unusually tired with many experiencing difficulty in reading and coordinating their leg movements during the stepping stool exercise;
- pulse rate increased after the dose of atropine, and increased more after the larger doses;
- changes in blood pressure and ECG were not consistent from subject to subject;
- resting rectal temperatures were slightly raised.

This study suggested that atropine caused a fall in blood sugar levels in those men who fasted. This was investigated further. Thirteen men fasted but ingested 50 g of glucose at 10 o'clock on two successive days. On the second day, one hour before taking glucose, 5 men were given a dose of 2 mg of atropine and 8 a dose of 5 mg. The blood sugar levels of all responded in a similar way.

Atropine was also given orally in 30 ml of water. Sixteen men took part. Pulse, blood pressure and pupil size were measured before and at various times after dosing. The doses used and observations made are listed below.

- Five men had a dose of 2 mg on one day, then two more doses of 2 mg (with 4.5 hours between the doses) on the next day. All complained of a dryness of the mouth which persisted for 2-3 hours. Changes in pulse and blood pressure were negligible after each dose.
- Six men had two 3 mg doses (with 2 hours between doses). The first dose produced a definite increase in pulse rate, which was most marked one hour after dosing and after 2 hours had almost returned to pre-dosing levels. The second dose then raised the pulse again to about the same level. Small changes were observed in blood pressure but felt to be of no clinical importance. Two men complained of difficulty in urinating after the second dose.
- Five men had a single 5 mg dose and experienced a more marked increase in pulse rate than their counterpart. Here the pulse rose by 50% within 45 minutes, returning to pre-dosing levels a little more than 6 hours afterwards. Slight falls were observed in systolic and diastolic blood pressure. One man complained of difficulty in urinating, two men of dizziness.

Some work was carried out to investigate tolerance. Five men had a dose of 2 mg each morning for 5 successive days and 5 men had a 2 mg dose morning and afternoon for 3 days. No evidence of men developing a tolerance to atropine was found.

The main conclusion of the study was that a dose of 2 mg seemed reasonable whereas a dose of 5 mg, in the absence of nerve agent intoxication, may "produce embarrassing effects which may be significant in troops with operational responsibilities" [8]. Work in September 1952 [9] explored the effect of atropine on the military efficiency of 235 volunteers from the 1st Battalion Royal Scots Fusiliers in field trials held at the All Arms Training Centre in Sennelager, Germany. Four trials were held, featuring different military skills: an approach march followed by a simulated attack; rifle and Bren gun firing on the range; a simulated attack in twilight; and night patrolling using compasses. The majority of the men, 196, received a 2 mg dose of atropine by IM injection but, for comparison, 22 men had a dose of 4 mg and 17 a dose of saline.

The conclusion of the work [9] was that 2 mg seemed to be the maximum permissible dose by IM injection. Even this dose may cause some embarrassment from dryness of the mouth (which made giving orders difficult), fatigue, giddiness and the consequent difficulty these symptoms induced in handling instruments. When the results were reviewed in November 1952 [10] it was agreed that a 2 mg dose of atropine by IM injection seemed suitable for

temperate climates but the effect of atropine in tropical conditions needed to be explored. The next series of studies addressed this issue.

The first trial, involving 51 volunteers, explored the effect of atropine on acclimatisation to hot and dry (110° F and 30-40% relative humidity) and warm and moist (95° F and 95% relative humidity) conditions. The conditions were produced in the climatic chamber, wherein the men spent 4 hours each day for five or 10 days, either resting or performing short periods of work on stepping stools. On the fifth day or the tenth day, each man received a dose of atropine by IM injection of either 1 mg or 2 mg. Some of the men were not given atropine but another possible therapeutic agent called BW 182³. These men had the recommended therapeutic dose of BW 182, 5 mg, by IM injection. Some men continued their acclimatisation beyond the fifth day and, on the tenth, received another dose of atropine or BW 182. Another 12 volunteers served as controls at normal room temperature.

Samples of sweat were collected from each man. Blood pressure, pulse rate and rectal temperatures were taken, and urine collected. The study observed [10] that atropine (and BW 182) disturbed acclimatisation by increasing the pulse rate and decreasing the rate of sweating, although the disturbance was less in warm/moist conditions than in hot/dry conditions. The next trial considered the effect of atropine on men who had already acclimatised and was conducted at UK bases in Iraq and the Far East [12].

In June 1953 twenty-five volunteers took part in trials over an obstacle course at the RAF station at Habbaniya in Iraq. Trials were held on four days with each man taking part in two trials (either on days 1 and 3, or on days 2 and 4). During each trial the men completed the obstacle course twice. Their blood pressure and pulse was measured before and after each round. In each trial some men served as controls, and were given saline by IM injection, while the other men received doses of either 1 mg or 2 mg of atropine by IM injection. Water intake was controlled: some men being allowed to drink as much as they wished before and during the trials; others being allowed no water either during or before or at any time. The points drawn from the work were [12]:

- the effect of atropine was not normally felt for about 30 minutes but after that it was easy to discern those men who had been given atropine by the flushing of their faces;
- some men collapsed or became incapable of continuing round the obstacle course and were immediately placed at rest in the station hospital, where a short rest halted the rise in their temperature;
- men thus treated were generally able to rejoin their group within 60-90 minutes of collapsing.

The conclusions drawn [12] from these trials in Iraq was that a 2 mg dose was harmful to men exercising in a warm dry climate. A large proportion could be expected to collapse and would be useless as fighting men. After a dose of 1 mg of atropine, about 10-15% of men could be expected to collapse.

The trials in the Far East were held at the jungle training ground in Malaya and on Singapore Island [12]. Twenty six volunteers drawn from local Army units took part in trials on the training ground which involved patrolling, a simulated ambush and road march. Thirty six men took part in a night patrolling exercise on Singapore Island. Most of the 62 volunteers had a dose of either 1 mg or 2 mg of atropine given by IM injection, a few had saline and served as controls. The observations made during these trials were [12]:

- men at rest remained alert and efficient after 2 mg of atropine, both in the hot day sun or the warm humidity of night;

³ BW182 was used as a medicine. It was referred to as the hydrobromide dihydrate of 1:1 diphenyl-3-piperidine butyramide.

- some men on patrol collapsed after a dose of 2 mg of atropine, and the effects of atropine on marching men were more marked.

In summarising the findings from these trials in Iraq and the Far East, Porton made the following points [12].

- The trials show conclusively that 2 mg of atropine cannot be tolerated by many men in these climates, and even the effects of a 1 mg dose of atropine were too pronounced to justify "unqualified general issue of 1 mg of atropine sulphate to all troops in the tropics."
- Nevertheless, nerve agents were more effective in the tropics so a "good" dose of atropine was necessary.
- The previously held assumption "that most servicemen would not be able to detect for certain that they had been exposed to a G agent" may not be true, particularly for exposure to vapour which induces marked symptoms (tightness of the chest, miosis etc.) fairly quickly. Therefore, there may not be many occasions where men gave themselves atropine in the absence of nerve gas poisoning. It was recognised, however, that the symptoms following exposure to liquid G agents on skin were much vaguer.
- Overall, the dose of 2 mg of atropine should be retained and it should be accepted that "if some [healthy men] inject themselves when they have not been exposed to a G-agent then this would be the price which may have to be paid to ensure that the lives of many of those who have been exposed are saved."

The BC, in reviewing this work in January 1954, were worried about the effect of atropine in tropical conditions [13] and noted that substitutes for atropine were being explored. Among these were oximes (from which P₂S would eventually emerge). Further work was carried out at Porton on the effect of a 2mg IM injection of atropine.

- The first study in 1954 looked again at the effect of atropine on acclimatisation [14] and repeated the procedure used in the earlier work. Sixty four men took part, exercising in a temperate or warm/moist or hot/dry climate for 5 or 10 days. Each man had a 2 mg dose of atropine on the 5th or 10th day. Many measurements were taken including blood pressure, pulse, temperature, respiratory performance, and sweat loss. In addition, the content of excretion was analysed. The findings of the previous study were confirmed (atropine hampers acclimatisation) but the main conclusion was that men in hot/dry climates who were given a 2 mg dose of atropine would for about 2 hours be "casualties from the effects of the drug."
- The second study, exploring the effects of atropine on men "with some degree of naturally acquired acclimatisation", was conducted at the Hot Climate Physiological Research Unit at Oshodi in Nigeria [15]. Five African volunteers from the Nigerian Regiment took part. One man acted as a control and received no atropine; the remaining 4 were given three doses of atropine (two doses of 2 mg and one dose of 1.2 mg) over four days. The men exercised in a similar fashion to those who had participated in trials at Porton. The men were able to complete fairly strenuous and prolonged exercise after atropine.

A field exercise was conducted in 1955 to explore the combined effects of a 2 mg dose of atropine and the wearing of respirators on military efficiency. The exercise was called "Hangover II", and featured volunteers from the 1st Battalion the Wiltshire Regiment (Duke of Edinburgh's). In the first part of the exercise, most volunteers were exposed to GB (some were not and served as controls) and then performed a military exercise under various conditions, as summarised in Table 19.1.

Condition	No. of men exposed to GB	GB dose (mg.min/m ³) (t = 2 mins)	No. of men as controls
No treatment	31	12.0	9
2 mg of Atropine IM	33	11.4	11
Wearing respirator	40	12.8	14
Atropine and respirator	45	11.8	12

Table 19.1. Part 1 of Exercise Hangover II.

In the second part 20 men performed a simple night patrol after being exposed to a dose of GB of 13.3 mg.min/m³ (t = 2 minutes). Ten men received no atropine and the other 10 received a dose of 2 mg IM of atropine. The conclusions drawn from the exercise were [16] as follows.

- 2 mg of atropine impairs eyesight and mental alertness so much that operations such as patrolling by day may be hazardous and would be definitely dangerous at night.
- Wearing a respirator increases the mental harassment (lack of concentration, shortness of temper and irritability) induced by GB and produces distress during intense physical effort.
- The effects of taking a 2 mg dose of atropine and wearing a respirator are practically additive; nonetheless troops must protect themselves in this way after being exposed to a G agent.

Despite the difficulties induced by 2 mg IM of atropine revealed by this exercise and previous trials, this dose was preferred. During 1955 Porton conducted a large investigation of the effects of this dose on the various systems of the body [17]. The effect of atropine on the following was covered:

- eyesight (10 volunteers participating);
- metabolic rate (10 volunteers);
- fitness for hard muscular work for a short duration on a treadmill (120 volunteers);
- fitness for work of increasing intensity for a short time on a treadmill (10 volunteers);
- fitness for prolonged muscular work on stepping stools (10 volunteers);
- posture and circulation with men on a tilt table in various positions (10 volunteers);
- posture and pulse and blood pressure in tilt table studies (6 volunteers);
- pooling of blood in different parts of the body (10 volunteers);
- skin temperature in tilt table studies (10 volunteers);
- limb volume, measure by gently placing arm or leg in water and measuring the amount displaced (20 volunteers);
- cardiac output in upright and level positions (10 volunteers);
- circulation time, measured by injecting 3 ml of 20% Decholin into a vein and noting the time taken for men to experience a bitter taste (10 volunteers);

- EEG (10 volunteers);
- reaction time, by measuring a man's reaction to a light or sound (10 volunteers);
- local circulation, measured by monitoring the clearance rate of radio-active sodium from the site of the atropine injection (10 volunteers).

These investigations produced the following points [17]:

- distant vision is not affected by 2 mg of atropine but some restriction of the near vision occurs;
- work of moderate intensity can be performed effectively after this dose but efficiency is lost in heavy muscular work;
- major circulatory changes induced include an increase in pulse rate and the lowering of blood pressure and cardiac output;
- the CNS appears to be generally depressed from the results of the EEG work and reaction times.

In December 1955 the BC concluded that a dose of 2 mg of atropine should be selected as immediate therapy for nerve agent poisoning [18].

19.1.3. Route and method of atropine administration

The selection in late 1955 of a dose of 2 mg of atropine as immediate therapy assumed that it would be given by IM injection. Indeed, IM injection was favoured from the outset as being one of the easier routes for untrained soldiers to use although some studies were conducted to compare different routes of administration.

The first human study of atropine, which reported in 1952 [8], included administration by oral and IM routes from which it was concluded that the IM route was much more rapid and effective than the oral route [19]. A comparison of IM, subcutaneous and IV routes was carried out in 1952/1953, involving 60 volunteers [19]. Each volunteer had doses of atropine by all three routes on successive days. Twenty men received doses of 1 mg by subcutaneous injection, 1 mg IM and 0.5 mg IV. The other 40 men were given doses of twice those amounts. The men were given these doses while resting. Twenty other men received doses of 2 mg subcutaneously and 2 mg IM on separate occasions and then walked on a treadmill for 30 minutes. The increase in pulse rate was used as the main index of the rate at which atropine was absorbed. The results were:

- IV produced the most rapid effect, the magnitude of the increase in pulse rate after a dose of 1 mg given by IV injection was similar to the increase after 2 mg IM or subcutaneously [19];
- the subcutaneous was more effective than IM injection.

Despite these benefits, IM injection was far easier to administer for Service personnel than either of the other two routes. A short study was conducted to explore whether taking atropine orally could sustain the protection given by an IM dose of atropine [19]. Six men took part and were given an initial dose of 2 mg IM and 2 mg oral (in 100 ml of water), followed by further 2 mg oral doses 1, 2 and 3 hours later. All complained of tiredness after 2 hours and after 3 hours all experienced difficulty in urinating.

The need for atropine to be given quickly after exposure to a G agent and the preferred route of IM injection meant that self-injection devices suitable for use by Service personnel had to be developed and tested. The first study of candidate devices reported in 1952 [20].

Five devices were tested in two trials in which 44 RN volunteers participated. All the devices required the needle to be inserted into muscle and four of them then required a pouch containing the liquid to be squeezed. The objective of the trials was explained in an "Instructor's Talk", which is given verbatim in an appendix to the study report and reproduced below [20]⁴.

"This test which we want you to do is a very important one. We need your full co-operation since you are going to do the test; we are only going to watch you. Let me explain how important the test is and what we want you to do.

If an enemy should use "nerve gas" against you and you got a "killing dose" then you would die in five to ten minutes. Fortunately, we have found a remedy which if given quickly enough will completely protect you from the killing dose. We have something which will save your life and those of other servicemen and of the civil population. But, since once you've breathed the nerve gas, you are going to die within a matter of minutes, the remedy must be given quickly – within a minute or two of you breathing the gas. We can't have doctors and stretcher bearers rushing round to you all - there wouldn't be enough doctors or bearers. So you must give the remedy to yourselves.

The snag is that the remedy has to be injected. You have to stick a needle into yourself to save your life.

We want to find out whether you can do it and how quickly and efficiently you can do it. We'll teach you how to put the needle in. If it is done properly then it won't hurt you. In addition you must get all the solution in. We'll teach you how. The solution you are using is quite harmless."

Each man made a trial injection into the thigh of a stuffed dummy and any mistakes made were corrected. In the first trial, four of the devices were tested by 24 men. Each man tried one of the devices on each of 4 successive days, on each occasion injecting himself in the middle of the outer side of the right thigh. Three of the devices were filled with saline, one with 1.2 mg of atropine. The second trial compared the fifth device with the one of the others, and 20 men tried both on successive days. The men were asked which device they preferred. The points made included [20]:

- any of the 5 devices could be prepared and self-injected within a reasonable time;
- the "Ampin" device was most easily prepared and inserted, and delivered the largest proportion of its liquid content (this was the device that did not require the man to squeeze a container to discharge the liquid into his thigh muscle).

As time went on, devices were developed which were easier to use. The "ACE injector", developed at the Harvard School of Public Health, was tested in 1954 [13] but the cost of production (30-40 cents) was thought to be too high. Porton developed a "semi-automatic injector", in which a hidden needle broke through a seal when pressed against the thigh [16]. This device was tried by 78 men during Trial Hangover II but 21 failures occurred, mostly because the device was placed against the thigh with inadequate pressure. The trial concluded that a fully automatic device was required, which both inserted the needle into the thigh and injected the contents without too much effort from the man using it [16].

The first such device, developed in 1955 [21], was the "Autoject". It was compared with a trade-produced device in human studies in 1956, in which Servicemen expressed a preference for it [22], and two different variants of it were tested in 1957 [23]. In 1958, the Model IV Autoject was accepted by the War Office as the Mark 1 Design, and this was tested in a troop trial in Germany in January 1962 [24]. Some problems emerged from this troop trial

⁴ This is the only Porton report reviewed by the survey which includes a verbatim briefing.

and the Model V Autoject was developed in 1962/63 [25]. Tests with this model were conducted with 122 volunteers in 1964 [26].

Between September 1964 [27] and July 1965 [28] a further 50 volunteers took part in a study to test if they could use the Autoject efficiently after they had been exposed to GB. None of the men had used an Autoject before and all received instructions before the study in how to use it. Some of the men were allowed to try the Autoject on a dummy before using it on themselves while the remainder relied only upon the verbal instructions [29]. The study involved 25 of the men giving themselves an Autoject injection during their first week at Porton and another during their second week immediately after a exposure to GB of 5 mg.min/m³ (t = 30 minutes). To explore how GB affected the ease with which Autoject could be used by men who had never used them before, the other 25 had this regime reversed [28].

The Autoject, containing 2 mg of atropine, was adopted as the immediate therapy device and it was intended in 1961 to give each Serviceman and woman two Autojects [30]. The BC discussion of this intention in November 1961 [30] sparked a debate on how much atropine should be given, and the results of studies of the effects of atropine in the tropics were raised. It was agreed that the Services should decide when and how Autojects should be administered following the initial injection of 2 mg of atropine.

By 1968 it had been decided that each member of the Armed Services should be given 3 Autojects. A field trial was conducted in June 1968 to find out the effects induced if man was to administer 3 Autojects (a total of 6 mg of atropine) to himself without having been exposed to nerve gas [31]. The trial took place over three days. On each day various tasks were performed: digging foxholes; map reading and taking compass bearings; rifle shooting; changing the rear wheel of a Land Rover; locating and handling two dummy casualties.

Thirty one volunteers took part with 8 of them acting as controls and receiving no atropine. The remaining 23 injected themselves with an Autoject at 20 minute intervals on the second day. All injections were made in the upper/outer thigh through material which was previously cleaned with alcohol. Each man was fitted with a rectal probe so that body temperature could be monitored and all were encouraged to maintain a high fluid intake. The observations made during the trial were [31]:

- performance of the tasks seemed to have recovered on the third day;
- only 2 relatively unaffected men ate lunch on the second day (after the atropine injections), the others eating only snack items;
- one man's temperature rose to 103° F and he was withdrawn from the task he was performing;
- ten of the 23 men experienced disorders of perception 2-6 hours after the third injection, including visual or auditory hallucinations (7 men), hallucinations of taste (2 men, believed clean water tasted salty) and colour distortion (one man perceived grass to be blue);
- one man became disorientated and was unable to co-ordinate voluntary movements (ataxia) one hour after the third injection and was removed to the station hospital where he recovered completely without treatment 8.5 hours later.

The work concluded that 6 mg of atropine may be expected to incapacitate. Instructions in the use of atropine emphasised that injections after the first one should be administered only if particular symptoms were experienced [32].

19.2. P₂S studies: 1954 - 1971

19.2.1. Introduction

Concern about the effect of atropine on men in tropical climates was in part responsible for a search for alternative treatments [13] from 1954 onwards. Hydroxamic acids were investigated [33] as they were thought to reverse the activity of anti-ChE agents. Much animal work was conducted with these acids and with oximes. In 1954 animal studies suggested that although atropine protected animals against large doses of GB those deaths that did occur were due to neuro-muscular block, which atropine did not affect [34]. Oximes were found to reverse neuro-muscular block [35] by reactivating inhibited ChE [34]. Indeed, this was the first time a class of compounds had been found that "could restore ChE" [34]. Further work with animals in 1955 showed that oximes and atropine together were extremely effective in treating nerve agent poisoning; more than 40 times the lethal dose of GB could be survived by rats [18].

Nevertheless, oximes were found to be toxic because they produced cyanide in the body [18]. Animal studies investigated many oximes in the quest for one which would not be too toxic for man and these studies ran on into 1957 when P₂S was discovered [36]. Animal studies were undertaken to investigate the effectiveness of combinations of P₂S and atropine [37] and the toxicity of P₂S [38]. The resulting report, produced in 1958, suggested that the optimum safe dose for man was 30 mg/kg IM [39].

A short human study was conducted to assess the dose of P₂S which could be administered by IM injection without much pain [40]. It was prefaced by animal work to determine what concentration of P₂S could be given without any muscle damage at the site of the injection. Animals were also given different concentrations of saline. The animal work showed that a 25% concentration of P₂S in 2 ml caused no damage and neither did a 7.5% concentration of saline. The human study used this equivalence and 29 volunteers receiving 44 injections (15 volunteers had two injections) of saline of concentrations progressing from 1% to 8% and in a volume of 1 ml, 1.5 ml or 2 ml. A crude test of performance was conducted for the volunteers who received concentrations of 6-8%. Before and after the injection, each man were asked to jump as high as he could from one leg (the one into which the injection was given) and make a mark on the wall with an inky finger. The conclusions, reported in 1958, were [40]:

- 6% saline in 2 ml caused no pain, and concentrations of 8% caused no undue pain;
- therefore, given the equivalence found in the animal work, it should be possible for a man to have an IM injection of 25% P₂S (500 mg in 2 ml) without pain.

Despite this result, the absorption into the body of P₂S from an IM injection was thought to be too fast and the slower rate of absorption from taking P₂S orally was preferred [39]. Work on the oral administration of P₂S was conducted with animals [41], using a dose of 200 mg/kg 1-2 hours before 15 times the lethal dose of a V agent was given. P₂S given as a prophylactic, and supplemented by atropine 1 minute after the dose of V was given, saved the lives of more than three-quarters of the animals. The protective effect of P₂S was found to begin to wear off after about 2 hours.

The human studies conducted with P₂S thereafter until the mid-1960s concentrated on the oral administration of P₂S as a prophylactic. Studies explored dose levels effective against GB, dosing regimes and the design of tablets used to administer P₂S. Later work into the 1970s considered P₂S additionally as an adjunct to atropine as an immediate treatment. This work initially considered P₂S being taken as tablets alongside atropine injections but later human studies developed and assessed a combined solution of atropine and P₂S for Autojects.

19.2.2. P₂S doses levels against GB

The first oral P₂S human study carried out in 1959/1960 sought to explore the effect of the drug when given as a prophylactic on ChE inhibition after exposure to GB [42]. Animal work had shown that small daily oral doses of P₂S produced few effects [42] and that the largest dose of P₂S found to be non-toxic was 100 mg/kg, the equivalent of 7 g for a man of average weight. Eighty five men took part in the study with 11 being given an oral dose of 3 g (thought at the time to be the "probable minimum effective dose" [42]), 21 men had a dose of 4.5 g and 23 men a dose of 7 g. The remaining 30 men, acting as controls, received placebos. All 85 men were exposed to GB, 15 mg.min/m³ (t = 15 minutes), three hours after taking the P₂S.

The men wore no respiratory protection during the exposure and walked at a steady 3 mph to ensure a steady breathing rate. ChE measurements were made before and at various times after exposure. The points made by the study are listed below [42].

- Blood ChE levels of the men given P₂S were significantly higher than the controls immediately after the exposure to GB and continued to be higher over the next 6 hours.
- There was generally no difference in blood ChE levels between different doses of P₂S. It was thought this might be because P₂S was absorbed only slowly or because the necessary and effective dose was less than the smallest dose used here. Future studies ought to consider doses smaller than 3 g.
- There was little doubt that P₂S could have been a useful prophylactic against GB.

The next study explored the effect of P₂S on the symptoms induced by GB (although ChE measurements were taken as well) [43]. Here a single dose of 3 g of P₂S was used but doses were also given after an exposure to GB of 15 mg.min/m³ (t = 15 minutes). Sixty five men took part; 48 men had a 3 g dose of P₂S 3 hours before being exposed to GB and then two further 3 g doses 12 hours and 24 hours afterwards. The remaining 17 men served as controls. Some men kept their eyes closed (at the behest of Porton staff) during the exposure to GB. The conclusions drawn were [43]:

- compared to the controls, P₂S diminished the incidence and persistence of the major symptoms;
- ChE inhibition in controls was found to be about 50% immediately after the GB exposure and those men who had taken P₂S had ChE depressions which were nearly as great;
- however, the ChE of the men dosed with P₂S recovered considerably faster than the controls in the subsequent 24 hours.

The third study in this series varied the delay between taking P₂S orally and being exposed to GB [44]. The previous studies had involved men taking P₂S three hours before exposure to GB; here 48 men took P₂S one hour before and 12 men took P₂S twelve hours before. The 48 men were split into equal groups of 12 and given different doses of P₂S; 1 g, 3 g, 4.5 g and 7 g. The 12 men receiving P₂S twelve hours before were given 7 g. All 60 men, and another 12 who had not been given P₂S, were exposed to 15 mg.min/m³ GB (t = 15 minutes). The conclusions drawn were [44]:

- in all cases ChE depression was about 50% immediately after the GB exposure;
- P₂S given 12 hours before exposure had no effect on the recovery of ChE but doses of 3 g and above given one hour before exposure resulted in a recovery of ChE three hours after exposure twice as high as observed in controls;

- six hours after exposure all the men who had taken P₂S were free of the symptoms associated with GB but the controls were still complaining of a tight chest and running nose.

The report noted that although P₂S was given before the exposure it seemed to act therapeutically rather than as a prophylactic: all studies had shown P₂S had no effect on ChE inhibition immediately after GB [44]. This point was accepted by the BC in 1962 [45] but taking P₂S orally as a prophylactic was thought to give "instant therapy with the oxime ready in the blood to reactivate quickly the inhibited enzyme [ChE]".

As was mentioned in the chapters dealing with nerve agent studies, GF was used in human tests in 1963. During the autumn and winter of 1963 volunteers took part in a study to investigate the value of P₂S as a prophylactic against GF [46, 47]. Thirty men took part, following work with animals [46], and received the following doses (in all cases P₂S was taken one hour before a single breath exposure to GF) [47]:

- 3 g P₂S tablets and a single breath exposure of 1.56 µg/kg (10 men);
- 7g P₂S tablets and a single breath exposure of 1.89 µg/kg (6 men);
- 7g P₂S capsules and a single breath exposure of 1.24 µg/kg (14 men).

19.2.3. P₂S dosing regime and tablet design

Attention then turned to the necessary dosing regime and the design of tablets. Animal work had shown that 4 µg of P₂S per ml of plasma in blood was the critical concentration for surviving an exposure of 10 times LD₅₀ of GB or VX (providing that atropine was given after exposure) [48]. Various studies were conducted to establish the design and formulation of tablets which would produce and maintain this P₂S concentration in man. Tablets containing 1 g of P₂S were considered in different formulations.

Initial work showed that conventional coated tablets were not suitable because P₂S had a bitter taste and was very soluble [49].

Studies explored gelatine capsules (containing 1 g of powdered P₂S) and various uncoated 1 g tablets which released P₂S quickly or slowly [49]. The 39 men who tried these tablets were given a total of 7 g of P₂S. The work showed that a mixture of slow and quick release tablets was effective, so another 8 men took a mixed formulation comprising a total dose of 4 g and another 13 men a mix totalling 3 g [49].

Further studies, involving 23 men, were carried out at doses of 4 g with a mix of slow and quick release tablets of different formulations, including a double layer tablet which contained a slow release and a quick release component.

This work suggested that a dose of four 1 g tablets (3 slow release and 1 quick release) would produce and maintain the required concentration of P₂S in plasma [49]. The next study in 1964-66 explored the oral administration of P₂S at regular intervals for several days [50]. Much of this study involved men taking P₂S in various forms of tablet for periods of up to 14 days, at intervals of 4-6 hours. Initial work saw 36 men take P₂S for up to 3 days and, when no unpleasant effects were observed, 10 men took 4 g of P₂S every six hours for 14 days and 9 men took 3 g every six hours for 10 days [50]. Clinical trials were then conducted for evidence of signs of toxicity, in which 243 men took P₂S for up to 14 days. The results were [50]:

- doses of 3-4 g of P₂S taken every 6 hours will maintain the necessary plasma concentration and 4 g doses would be preferred;

- the toxic effects of prolonged dosing with P₂S are confined largely to alterations in the pattern of bowel movements⁵ but not to the extent of causing inconvenience;
- other symptoms of prolonged dosing were mild and no haematological or biochemical abnormalities were observed.

As part of this work 5 men, who had taken three 1 g double layer P₂S tablets every 6 hours for 10 days, were exposed to a GB concentration of 0.5 mg/m³ for 30 minutes one hour after their final P₂S dose. Their ChE recovery after exposure was faster than other men who had been exposed to GB (as part of another study) but who had not taken P₂S; the men who had taken P₂S also felt better than those who had not.

A short study was conducted to compare the release of P₂S from slow and rapid tablets produced from a commercial source, as the US claimed that the tablets showed no difference in release rate. The study, in which 51 volunteers took 4 g of slow and quick release pills, confirmed the tablets released P₂S at different rates [51]. Aside from this brief diversion, the next study considered the ease with which 1 g tablets could be taken and was conducted in 1967/68 [52], prompted by the Army expressing concern that 1 g tablets were too large to take comfortably [53].

The study [54] used glucose tablets similar in appearance and volume to the P₂S tablets which were being proposed for the Services. The first part of the study considered how easy it was to swallow different shapes of tablet (thick, fat, and long) and was completed with 39 volunteers (12 of whom were women) from Porton's civilian laboratory staff. Eighteen were allowed to have water to take tablets with. Most were able to swallow the tablets without water but tablets were taken faster by those who had water available.

The second part of the study, involving 39 male Service volunteers and 21 females from the civilian laboratory staff, considered how much water was required. Each took glucose tablets without water and then with 30 ml and 60 ml of water. Men were able to swallow the tablets more easily than women, for whom water helped considerably. The availability of water produced no significant change in the men's tablet taking.

Water might not be available in the field, so the third part of the study examined the ability of Service volunteers to take 1g glucose tablets without water. This part of the study adopted the drill proposed for tablet swallowing in contaminated environments. The 101 volunteers who took part wore full protective equipment. Four 1g tablets were carried in a plastic dispenser specially designed to reduce the time taken to handle tablets. The drill was to remove the cap of the dispenser, close the eyes, hold the breath, raise the respirator with one hand and with the other shoot tablets from the dispenser into the mouth, and then replace the respirator. All four tablets were successfully swallowed using this drill by 91 of the men in an average time of about 25 seconds. Ten men were unable to swallow all four but nine of these men managed it when water was available.

The main conclusions of this work were [54]:

- the shape of the tablets has only a marginal effect;
- about 10% of men and 30% of women may be unable to swallow tablets without water, and 2% of men may not be able to swallow 1 g tablets at all.

The final study in this series of oral P₂S investigations before P₂S was accepted for use by the Services considered how tablets should be stored so that they retained their effectiveness [55]. The study, conducted in 1967/68 [52], involved one group of men taking four 1 g P₂S tablets which had been stored for up to 6 weeks, and a second group of men taking a 4 g

⁵ During this trial, tests were conducted to determine whether the nature of the oxime salt affected bowel activity. P₂S is the methane sulphonate salt of an oxime referred to as PAM. 10 men were given the chloride salt of PAM, instead of P₂S.

dose (of tablets which had been stored at different temperatures for either 12 weeks or 24 weeks [55]) daily for four days. The conclusions drawn were:

- judging by the plasma P₂S concentration, none of the stored tablets became inactive and it was recommended that tablets were stored at room temperature or below;
- half of the men who took P₂S for 4 days complained of looseness of stools but they were able to carry out their duties elsewhere without impairment.

P₂S was accepted for use by the Services in 1969 [56]. The treatment for nerve agent poisoning based on P₂S and atropine, recommended by the ABC in 1968, is [32] summarised below.

- On coming under risk of attack with nerve agents, take four 1 g tablets of P₂S every six hours.
- After inhaling nerve agent, take four more tablets of P₂S and self-inject 2 mg of atropine with an Autoject. Atropine should be given every 15 minutes and P₂S every four hours until symptoms disappear.
- After liquid contamination, take four 1 g tablets of P₂S and repeat every six hours. Six hours after contamination take 2 mg of atropine with an Autoject.

Despite this advice it was accepted that the precise manner in which P₂S was to be used would be subject to user trials conducted by the DNBCC [56]. The DNBCC completed an initial user trial in 1969 with 9 staff members taking 4 g of P₂S every six hours for 14 days [56]. As a result, the DNBCC claimed that diarrhoea occurred as a side-effect and was of such severity as to lower military efficiency [56]. In response, the ABC commissioned further human studies at Porton, which are outlined below. The studies examined bowel activity while P₂S was being taken and also assessed ophthalmic side effects.

- In a laboratory trial in 1970, 23 men took 4 g of P₂S every six hours for 14 days [57, 58]. Three men experienced diarrhoea to a degree sufficient to interfere with military duties but all recovered while continuing to take P₂S [57].
- In a field trial in July 1970, 58 men from the Royal Hussars took 4 g of P₂S every six hours for 14 days, and another 53 men were given placebo tablets [57]. The men continued their normal military duties and no apparent loss of military efficiency was observed by their commanding officer [57]. Only 2 men reported sick with incapacitating diarrhoea [57].
- Seven of the 81 men who took P₂S in these two trials experienced blurring of vision; a study of their medical histories suggested this might be a consequence of the men having poor accommodative power [58]. It was concluded that P₂S could be expected to cause blurred vision in individuals "susceptible to ocular symptoms" [58].

The ABC and CDAB, in reviewing this work, agreed that the advantages of P₂S as a treatment for nerve agent poisoning outweighed the disadvantages [57]. A final short study was conducted with oral P₂S in 1971 to confirm that the drug had no effect on the liver. Fourteen volunteers from Tidworth took 4 g of P₂S every six hours for 14 days [59]. No significant changes were observed in serum enzymes, from which the ABC concluded that the dosing regime of oral P₂S produced no clinical evidence of liver damage [59]. This concluded human studies of oral P₂S. It was intended to conduct a large scale trial with BAOR forces (Exercise Jeremiah) but this was deferred because the troops earmarked for the trial were transferred to Northern Ireland [59].

19.2.4. P₂S given IM with atropine

Taking tablets of P₂S as a therapy alongside atropine meant that men had to raise their respirators in contaminated environments and some might have difficulty swallowing the tablets. It would be more convenient if P₂S could be administered by IM injection.

The first study to examine P₂S by IM injection was carried out from 1967 to 1969 and had two parts.

- Fifty five men were given an IM dose of P₂S of 200 mg, 500 mg or 750 mg in 2 ml of solution. Blood samples were taken to monitor the P₂S concentration in plasma after the dose was given.
- Another 55 men took 4 g of P₂S orally and then, either 3 or 6 hours later, received an IM dose of P₂S of 200 mg, 500 mg or 750 mg [60].

The study concluded that an IM dose of at least 500 mg would be needed to produce the necessary plasma concentration of P₂S. The Autoject, used to administer atropine, contained 2 ml of solution into which 500 mg or 750 mg of P₂S could be incorporated. No adverse clinical effects were found in the men who took P₂S via IM injection after receiving an oral dose of P₂S. The study, therefore, cleared the way for P₂S, as a therapy, to be given with atropine as an IM injection rather than in the form of tablets.

The next study, carried out in 1969, explored whether a combined injection of P₂S and atropine affected the absorption of P₂S in the body [61]. Twelve men had an IM injection of 750 mg P₂S and 2 mg atropine in 2.5 ml and, five days later, another IM injection of 750 mg P₂S in 2.5 ml. These two injections allowed the absorption of P₂S to be compared, with and without atropine. Another 10 men had a similar regime but with a lower dose of P₂S (500 mg) and the injections given in 2 ml of solution. The conclusions of the study were:

- the combined injection has no significant effect on the absorption of P₂S;
- 500 mg of P₂S produced the required concentration in plasma within 10 minutes, whereas 750 mg of P₂S produced it in 3 minutes.

The next study, also completed in 1969, complemented the previous one by finding out if a combined atropine/P₂S injection affected the absorption of atropine in the body [62]. The rate of absorption of atropine was measured by the increases in pulse rate it induced (monitored continuously by ECG). The doses used in this study were identical to the previous one, except here atropine was given alone. Twenty two men took part and were given doses while they lay quietly. The study concluded that a combined atropine/P₂S IM injection did not reduce the rate at which atropine was absorbed into the body: indeed, for the first few minutes atropine absorption was increased.

This study was repeated but with men exercising on a bicycle ergometer [63]. Nine men took part. They cycled before and for periods (interspersed with rest) after IM injections. ECG was used to monitor heart rates, temperature was recorded and sweat loss measured. Each of the 9 men received IM injections of 750 mg P₂S in 2.5 ml of solution, 2 mg of atropine in 2.5 ml and a combined atropine (2 mg)/P₂S (750 mg) injection, with at least four days between each experiment with a drug. The points made by the study were:

- eight of the 9 men found the injection of P₂S alone more painful than either of the other two injections but the ache passed off within an hour and did not affect their performance;
- mixing P₂S and atropine had no significant effect on the absorption into the body of either.

By 1971 plans were progressing to change the Autoject so that it contained 2 mg of atropine and 500 mg of P₂S. The possibility of men giving themselves three Autoject IM injections in

the absence of nerve agent poisoning arose again. Here the concern was about the effects of taking 1500 mg of P₂S (3 times 500 mg), particularly after a regime of taking P₂S tablets as a prophylactic. A study in 1971 investigated these effects [64, 65]. Ten men took an oral dose of 4 g of P₂S and three hours later received two IM injections of 500 mg P₂S (with 20 minutes between the injections). Twenty two other men took an oral dose of 4 g of P₂S every six hours (the prophylactic dose regime) for 24 hours and three hours after the last dose received three IM injections of 500 mg P₂S. The observations made by the study were [64]:

- three IM injections of 500 mg P₂S taken after the oral prophylactic produced a high plasma concentration, well over that required, which was maintained for at least 3 hours;
- fifteen of the 22 men who had three IM injections experienced visual disturbances lasting from 5 minutes to a couple of hours, usually after the third injection, which included blurred vision when attempting to read small print and difficulty in focusing after moving the head.

In reviewing the results the ABC [65] noted that the visual disturbances were related to near point visions and would probably impair a man's ability to read instruments but distant vision was unlikely to be affected. Some concern was expressed about how this impairment would affect aircrew.

The change in near point vision induced by P₂S was contrary to the effect following exposure to GB, so it was possible they would cancel out when P₂S was used in IM injections as therapy after nerve agent exposure [66]. A short study was carried out in late 1971 [67] in which six volunteers were exposed to GB and, 40 minutes afterwards, given a 500 mg IM dose of P₂S. No report of this study has been found but a brief statement of the results from the first three men appears in COSHE meeting minutes. Apparently [67], shortly after receiving the P₂S dose the symptoms of GB poisoning disappeared although a degree of miosis was observed later.

These studies meant that, when given as a therapy in an environment containing nerve agents, P₂S could be administered as an IM injection with atropine from the same Autoject. This was much more convenient for Service personnel than using an Autoject for atropine and then taking P₂S tablets. It was also safer, as respirators had to be removed (albeit briefly) to take the tablets. However, the regime of treatments used by the Services was not changed for some while⁶. In 1975/6 Autojects were being modified for issue to the Services with combined contents of P₂S and atropine [68]. Further changes in the treatments were accepted by the Services in 1981 [69]. Those changes were based on human studies running from the early 1970s which developed and tested a new prophylactic (pyridostigmine) and made further changes to the immediate therapy of P₂S and atropine. Those studies are outlined in the next two sections.

19.3. Pyridostigmine⁷ as a new prophylactic

19.3.1. Introduction

P₂S was recognised in 1962 not to be a true prophylactic [45] but its use as such continued because the concentration of P₂S in plasma thus produced was ready as "instant therapy". P₂S had other shortcomings: in 1960 it was apparent that oximes (of which P₂S is one) were not effective against some nerve agents [70]. Oximes were found to be effective treatments for poisoning with GB and VX [71] but other G agents, notably GD, resisted oxime therapy.

By 1971 animal studies had been conducted to investigate the effectiveness of carbamates in treating poisoning by those nerve agents which did not respond to oxime therapy.

⁶ It is normal for equipment (in this case, treatments) to be introduced to Service use some years after it has been developed in research.

⁷ Throughout pyridostigmine is used to refer to pyridostigmine bromide.

Pyridostigmine was one of the two carbamates found to be the most effective [72]. It gave "appreciable protection" when given to animals as a prophylactic against GD poisoning [72]. Pyridostigmine when given as a prophylactic was found to produce in various animal species a complete recovery of neuro-muscular function following blockade by GD [73] (the recovery did not occur if pyridostigmine was not given until after the onset of GD poisoning).

When human studies with pyridostigmine began in 1971 it was noted [74] that pyridostigmine was used as a medicine for the treatment of myasthenia gravis, a chronic progressive disease in which muscles become tired, eventually progressing to muscular paralysis. Pyridostigmine is an anticholinesterase: it prevents the destruction of ACh, thus stimulating parts of the nervous system. This effect, useful in the treatment of myasthenia gravis, mirrors the effect of nerve agents. Like GB, for example, pyridostigmine will inhibit ChE activity, thus preventing the destruction of ACh.

As both pyridostigmine and nerve agents inhibit ChE, an explanation is warranted of how pyridostigmine is useful in treating nerve agent poisoning. Some background facts may be useful.

- ChE inhibited by pyridostigmine reactivates spontaneously. It will be seen that the dose of pyridostigmine as a prophylactic was chosen so that about 30-40% of RBC ChE was inhibited at any one time. But, over time, this was not the same ChE: in any instant some ChE inhibited by pyridostigmine became active, while other active ChE became inhibited.
- ChE inhibited by, for example, GB becomes active at a very much slower rate than ChE inhibited by pyridostigmine.

Figure 19.1 attempts to give a simple explanation of how pyridostigmine prevents death in men receiving a lethal dose of GB. It shows the ChE in the body as a block. Two sets of blocks are shown: one relating to the case where pyridostigmine is taken as a prophylactic and one where it is not. Active ChE is shown in grey; ChE inhibited by pyridostigmine (at a particular instant in time) is shown in yellow.

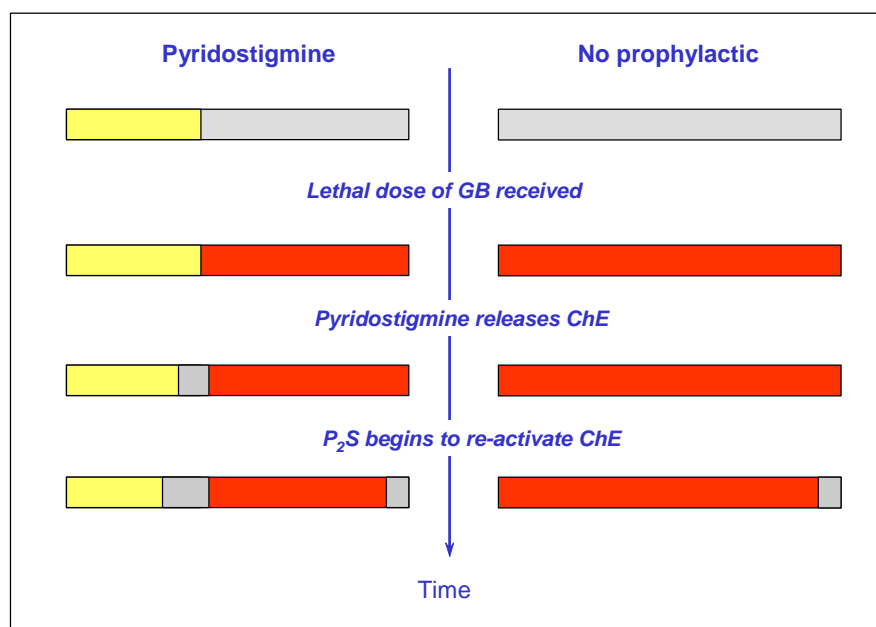


Figure 19.1. The action of pyridostigmine

The two blocks at the top of the figure represent the starting point. The sequence of events is depicted by lower blocks.

- A lethal dose of GB enters the body and the effect on ChE is shown in the second block. When no prophylactic is taken (right block), the lethal dose of GB will inhibit ChE entirely. Where some ChE is inhibited by pyridostigmine, it is protected from attack by GB. In that case the residual GB is destroyed either by chemicals in the body or by being broken down into harmless components by water in the body (called "hydrolysis").
- P₂S (and atropine) are given as therapies after the lethal dose has been received. It might be remembered from the description of P₂S studies, however, that P₂S takes time to re-activate ChE (men exposed to GB had similar ChE inhibitions immediately afterwards irrespective of whether they had taken P₂S or not). The third block represents a point in time shortly after the administration of P₂S. By this time, some of the ChE inhibited by pyridostigmine becomes active again (the grey section of the left block).
- The fourth block shows that, a little later, P₂S starts to reactivate the ChE inhibited by GB and ChE continues to be released after inhibition by pyridostigmine.

The middle two blocks show why pyridostigmine prevents death from lethal doses of GB. Man can survive if a small proportion of his body's ChE is active but with no ChE he will die. The figure also explains how pyridostigmine prevents death from GD. P₂S is not effective against GD, so the last block on the right would contain no free ChE at all.

The percentage RBC ChE inhibition aimed at for pyridostigmine (around 30-40%), when taken as a prophylactic, is chosen with several factors in mind: how quickly a nerve agent is destroyed in the body; the rate at which ChE inhibited by nerve agent becomes active again and the speed with which ChE inhibited by pyridostigmine is re-activated. It will be seen later that the percentage inhibition aimed at for another prophylactic, physostigmine, was different to that sought for pyridostigmine.

19.3.2. Pyridostigmine human studies

Human studies with pyridostigmine were first conducted in the period from 1971 to 1973 and explored the effects of single doses on physiology and in protecting against GB. The first study [75], noting that pyridostigmine was given in oral doses of up to 6 g when used as a medicine, used an oral dose of 60 mg. Fourteen volunteers were given this dose after breakfast. Various observations were then made every 30 minutes over the following 6 hours: ECG, blood pressure, temperature, near point vision, pupil size and area. ChE was also measured in whole blood, RBC and plasma. The study concluded that a 60 mg dose ought not to interfere with military performance as the effect on temperature and blood pressure was not significant and no subjective symptoms were reported by the volunteers. The pulse was slowed and small changes were observed in pupil size and near vision. These suggested that 60 mg was just above the "maximum sign free dose" [75].

The next study, carried out in late 1972 and early 1973, used a pyridostigmine dose of 30 mg and explored the effects following an exposure to GB [76]. RBC ChE was measured before and at various times (up to 72 hours) after the exposure to GB. The dose of pyridostigmine was given minutes before exposure to GB (5 mg.min/m³). Ophthalmic measurements were taken. Eighty four men took part: 28 were given 30 mg of pyridostigmine only; 28 received this dose and were exposed to GB; 28 received a placebo and were exposed to GB. The observations made by the study were [76]:

- the mean ChE depressions produced by pyridostigmine and GB separately were additive immediately after exposure to GB of those men who had taken pyridostigmine, and were about 50% [77];
- pyridostigmine has no effect on the ophthalmic effects induced by GB;

- no significant differences in ChE recovery after exposure to GB between those men who had taken pyridostigmine and those who had not.

That pyridostigmine had no effect on ChE recovery was explained as being a consequence of the exposure to only a low dose of GB: "It seem [sic] evident from animal studies ... that a positive demonstration of the benefits of pyridostigmine would require doses of nerve agent in excess of 1 x LD50" [76].

The next human studies were carried out in 1976 and 1977. Animal work up to 1976 had suggested that a dose of pyridostigmine which produced a blood ChE inhibition of 25-40% was likely to be most beneficial [78]. The studies in 1976 and 1977 sought to identify the dose regime of pyridostigmine which maintained this level of inhibition [79, 80].

One first study considered single doses [79] and sought to gain information on the distribution of pyridostigmine in the body, how it was eliminated from the body and the rate at which it was absorbed into the blood from the gastro-intestinal tract after being taken orally. Data on distribution was best obtained by administering pyridostigmine by IV injection and some preliminary work was conducted before the study started. Fifteen men received IV doses of between 0.2 and 1.0 mg [81, 82, 83]. The lowest dose caused no inhibition in RBC ChE, a 0.4 mg dose inhibited ChE by 10% [82] and a dose of 0.8 mg inhibited ChE by 20% [83]. The largest dose, received by 7 men, inhibited ChE by a maximum of 38% [81]. None of the 15 men experienced any symptoms.

After this preliminary work the study saw 16 volunteers receive an IV injection of between 0.6 and 1.5 mg [79]. Eight of those drank 40 ml of water containing 30 mg of pyridostigmine one week later and, one week after that, took 30 mg of pyridostigmine in tablet form. Four of the other 8 men who had IV injections took 60 mg tablets one week after their IV dose. To explore the effects of stomach contents on the adsorption of pyridostigmine, two other men took a 60 mg tablet without having breakfast first. Blood samples were taken from all the men (by IV cannula or by a needle depending on the volunteer's preference). The study gathered enough data so that computer models could be constructed which represented the absorption, distribution and elimination (commonly called "pharmacokinetics") of pyridostigmine [79].

The second study considered multiple doses [80]. Fourteen men took a 30 mg tablet of pyridostigmine every 6, 8 or 12 hours over three days. Two other men took 30 mg tablets every 8 hours over seven days. Blood samples were taken 3.5 hours after a tablet was taken and 10 minutes before the next one was due to be taken. The study concluded the following [80]:

- a 30 mg oral dose every 8 hours should protect a man from death from GD and other nerve agents and should be acceptable to the Services;
- further studies were required on the effect of pyridostigmine on long term health and the dosing regime should be tested with men engaged in their normal military duties.

The second conclusion led to a series of studies conducted during the period from 1979 to 1981 which involved men taking pyridostigmine while continuing their jobs at their bases. Before those studies started Porton conducted two studies to investigate any effect pyridostigmine might have on the liver and kidneys⁸ [84] and on performance [85]. Both studies used the dosing regime of 30 mg of pyridostigmine every 8 hours.

- The first study involved 12 men taking this dose over 10 days with 6 other men taking placebo (lactose) tablets as controls. None of the subjects complained of any symptoms and no abnormal constituents were found in their urine or physiological data, thereby indicating that the dose was unlikely to affect the liver, kidneys or bone marrow [84].

⁸ Two volunteers arrived a day late and only completed nine days on the drug.

- The second study featured 24 men taking pyridostigmine over 14 days with 12 other men taking placebos. A battery of tasks was used to measure the effect on performance, including the "Number Facility" test (volunteers had to add 2 one or two digit numbers read to them), grammatical reasoning, short term memory (writing down a sequence of digits after listening to them being read out), reaction time, attention tests, manual dexterity and muscular tests. None of the volunteers taking pyridostigmine showed any effects of behavioural significance and their performance in the mental and physical tests was unaffected (in most of the tests the performance improved after taking pyridostigmine) [85].

A number of studies with men at their own units were carried out in the period from September 1979 to November 1981. The men who participated gave blood samples periodically and completed some of the performance tasks listed above. The men who volunteered for these studies were split into two groups: one taking pyridostigmine, the other placebo tablets. The dosing regime of one 30 mg tablet every eight hours was used but the length of time the tablets were taken varied from study to study. Table 19.2 summarises these studies.

Base	Date	No. of volunteers		Length (days)	Comments
		pyrido	placebo		
Collingwood [86]	Sep 79	17	17	9-10	Some of the men were instructors at Collingwood, others trainees. 28 doses per man [86]
Cove [87]	Feb 80	14	10	21	Men were on training course involving moderately strenuous physical exercise (demolition, bridge-building, assault boat operations)
Shrivenham [88]	Nov-Dec 80	14	14	27-28	27 men were attending course at Shrivenham, the other was a member of the college staff.
Aldershot [89]	Jan-Feb 81	27	14	27-28	Some of the men took immediate therapy of atropine, P ₂ S and diazepam ⁹ at the end of the study [90]
Collingwood [89]	May-Jun 81	21	11	27-28	Some of the men took immediate treatment at the end of the study [90]
Borden [89]	Oct-Nov 81	15	10	27-28	Some of the men took immediate treatment at the end of the study [90]

Table 19.2. Pyridostigmine prolonged dosing studies at men's own units.

Only a few symptoms (listed below) were reported by the volunteers who took part in these studies.

- Some of men at Cove reported malaise. The course the men were on involved handling explosives, the fumes from which could have had this effect. Men in the pyridostigmine and the placebo group attributed their symptoms to this cause. No effects due to pyridostigmine were found in general behaviour and performance, nor were any other symptoms reported [87].
- Almost all the men in the Shrivenham study reported symptoms, with a running nose and an increased frequency of bowel movements being the significant ones reported by the men taking pyridostigmine. These symptoms were transient and,

⁹ The incorporation of diazepam into the previously developed immediate treatment of atropine and P₂S is covered in the next section.

at worst, caused only minor inconvenience. They were judged not to be militarily unacceptable [88].

Further studies were conducted during the same period. The first series, carried out at Porton, ran from the summer of 1979 and involved men taking pyridostigmine and being exposed to GB [91]. At the outset the computer model of pyridostigmine pharmacokinetics, generated after early studies, was used to predict the ChE inhibition expected in men taking the pyridostigmine dose and then being exposed to GB. The model predicted that an exposure to GB of 5 mg.min/m³, following pyridostigmine treatment, would induce a ChE inhibition of 20-35% [91]. This exposure of GB (with t = 15 minutes) was chosen for the study in which 18 men took part. Ten of the men took pyridostigmine, in the standard dosing regime, over 5-6 days, with the other 8 serving as placebos and taking placebo tablets. The work was carried out in 1979 and 1981. Twenty men took part in a study conducted over the period from 1980 to 1982 in which the same GB exposure level was used so that the effect on EEG could be assessed [92]. Ten of the men took pyridostigmine over 5 days and 10 men took placebo tablets.

Two studies considered the effects of heat on taking pyridostigmine. The first, in November and December 1979 [93, 94], involved men taking pyridostigmine over 16 days and exercising daily on a bicycle ergometer in a warm environment (30°C, 60% relative humidity) while wearing the full rig of protective clothing [93]. Four volunteers were to participate in this study [93] which was carried out in November and December [94].

The second study extended this work and was carried out in 1981 in the Environmental Medicine Unit (EMU) at the Institute of Naval Medicine in Alverstoke [90]. The aim was to investigate the interaction of prolonged pyridostigmine dosing and heat stress in men who had been acclimatised [95]. The volunteers spent 4 weeks in the climatic chamber at the EMU with the first week devoted to acclimatisation. In the middle two weeks the men took pyridostigmine, and completed various psychological and physiological tests which extended into the fourth week. Nineteen men took part in this study with 10 taking pyridostigmine and 9 taking placebo tablets. The climatic conditions used were 35°C and 55% relative humidity during the day and 22°C and 55% relative humidity at night [90]. The study is reported as being one of those conducted at men's own units [90] so, presumably, the 19 volunteers were drawn from the staff at Alverstoke.

The results from the studies with pyridostigmine conducted from 1976 were used to apply for a Product Licence from the DHSS. Following the introduction of the Medicines Act in 1968 [86], it became MOD policy to obtain a product licence for medical compounds [96]. The product licence for pyridostigmine to replace P₂S as the prophylactic for nerve agent therapy was granted and, in August 1981, the Services accepted pyridostigmine, referred to as Nerve Agent Pre-treatment Set (NAPS) [87].

19.4. Diazepam as an adjunct to atropine and P₂S immediate treatment

19.4.1. Introduction

Accepted by the Services alongside pyridostigmine in August 1981 was a new injection device to replace the Autoject. The new device had the same contents, 2 mg atropine and 500 mg P₂S, but was issued with a 5 mg tablet of Diazepam. Diazepam is a tranquilliser, known by various trade names (including Valium), and was introduced into medical use in the early 1960s. Animal work at Porton in the early 1970s demonstrated that diazepam improved the protection afforded by atropine against GB, VX and GD [97, 98, 99] by a factor of 1.5 to 6, depending on the species [98]. The value of diazepam was that it alleviated the tremors and convulsions induced by nerve agent poisoning [99].

A proposal to start human studies with diazepam was considered by COSHE in July 1973 [100]. A dose of 10 mg was suggested as it was the dose generally used by the medical profession for the treatment of epilepsy [100]. Human studies with diazepam ran from 11 July 1973 [101]. Initially the studies sought to understand the effect of diazepam alone and also

alongside atropine and P₂S. Later studies explored the effect of the three combined after pyridostigmine. Interspersed with this were studies of the new injection device. These three types of studies are covered in the next sections, thus bringing the story to the introduction of the new form of nerve agent treatment into Service use in 1981.

19.4.2. Diazepam studies

Between July and November 1973 sixty men took part in a study of the effect of P₂S and diazepam given by IM injection on reaction times, as measured by various psychomotor tests [101]. The men received P₂S and diazepam (5 mg or 10 mg) separately and together. After a pause in 1974 the work resumed from January to June 1975 [102]. As well as comparing P₂S and diazepam IM the study explored the effect of the solvent which allowed diazepam to be given as an IM injection [102]. Thirty three men took part in the 1975 element of the study [102]. The report of this work [103] covers 68 of the men who took part in the entire study from July 1973 to June 1975 (thus not citing the results from 25 of the men who took part). The report addresses the effect of diazepam on the rate of absorption of P₂S into the body and it is possible that this was not measured in the 25 men whose results are not included. The conclusions drawn by the study are listed below [103].

- A 10 mg dose of diazepam significantly decreased P₂S absorption for 30 minutes after the combination had been taken. A 5 mg dose significantly decreased P₂S absorption for 10 minutes.
- The solvent in which diazepam IM was given reduced the P₂S absorption rate significantly.
- The 27 men who received 10 mg diazepam IM complained of tiredness, inability to concentrate and unsteadiness of gait. All men complained of stiffness and pain at the IM injection site which persisted for up to 2 hours following the injection.

The study concluded [103] that diazepam would be better administered in an oral dose, partly because the IM dose produced a significant reduction in performance and partly because the solvent presently available to administer diazepam IM interfered with the absorption of P₂S.

The effect of an oral dose of 10 mg of diazepam on performance was explored in a study in 1975 [102, 104]. Twelve volunteers completed various psychomotor tasks (similar to those used in the pyridostigmine study mentioned earlier) and then took a tablet of either diazepam or vitamin C (as a placebo). The tasks were repeated regularly for 3 hours after the tablet was taken and again two days later. The points made by the study were [104]:

- there was no evidence that 10 mg oral diazepam caused serious incapacitation but the performance in all the tasks was reduced after dosing;
- all but one of the men reported subjective effects, most commonly a light-headed slightly drunken feeling;
- tasks involving thought and reasoning were more susceptible to the effects of diazepam and were likely to be affected for longer than motor control tasks.

The effect of combining atropine and diazepam on the rate at which atropine was absorbed into the body was explored in studies running from October 1975 [102] to April 1977 [105, 106]. The absorption of atropine was measured by the increase in heart rate. Volunteers who took part received atropine and diazepam separately and together. Diazepam was given either by IM injection of 5 mg or an oral dose of 10 mg [105, 106]. Thirty three Servicemen and 6 Servicewomen took part [102,105,106]. These studies were carried out in the laboratory with heart rate being measured continuously by ECG. Two further studies were conducted after April 1977 to complete the series and these are outlined below.

- In May 1977 the effect of atropine and diazepam on heart rate was explored in 6 men who, after taking either both or diazepam alone, completed a 5 mile route march [106].
- In July 1978 the effect of a 10 mg oral dose of diazepam on heart rate and blood pressure was explored in three Servicewomen, one of whom received a placebo and served as a control [106].

Some of the participants in this series of studies also performed psychomotor tasks and the results from these subjects were reported [107]. The report concluded that atropine and diazepam together were unlikely to cause a greater decrease in performance than atropine alone.

The next series of studies assessed the effects of the combination of atropine, P₂S and diazepam and ran from February 1976 to December 1980 [105, 108, 109]. The studies were split into two elements, detailed below.

- An assessment of the effect of the combination on heart rate, as measured by radio telemetry. In this element of the work the participants received the combination of atropine, P₂S and diazepam on one day and, on other days, atropine alone and P₂S alone. Usually 3 days elapsed between dose days [105]. Diazepam was given in an oral dose of either 5 mg or 10 mg. Twenty three men and 3 women took part in this work from February 1976 to July 1978 [105, 106]. A further 5 Servicewomen took part in this element of the work in 1980 [108].
- An assessment of the effect of the combination on psychomotor and cognitive performance. This element of the work was carried out in 1980 [109] and involved 45 volunteers. Thirty of the men took atropine and P₂S (given IM) and diazepam (given orally in either 5 mg or 10 mg) immediately afterwards. Fifteen men received placebo IM injections and tablets and served as controls [110].

The conclusions drawn from these studies [110] were as follows:

- a diazepam dose of 5 mg or 10 mg alongside atropine and P₂S will adversely affect attention, reasoning and manual dexterity;
- were more pronounced after a dose of 10 mg of diazepam;
- however, none of these effects was likely to incapacitate.

19.4.3. A change in injection device

Alongside this work with diazepam, studies considered the performance of the Autoject. These studies were prompted by concerns that the capsules containing atropine and P₂S used in the Autoject tended to leak or allowed the contents to evaporate during storage. Further, it was thought that, unless the capsules were stored below 4°C, the solution would become more alkaline and degrade the atropine and P₂S [111]. Twenty four men took part in a study in 1979 to compare the stored solution with a fresh solution of atropine and P₂S. The intention was to give each man an IM injection by an Autoject containing a stored capsule and, on another day, a fresh solution of atropine and P₂S by needle and syringe. In the event only 14 men received both as the mechanical firing of the Autoject failed several times. The comparison between the stored and fresh atropine/P₂S solution was made by monitoring the absorption of P₂S in blood (from blood samples regularly taken by an IV cannula inserted in a forearm vein) and the absorption of atropine (by measuring heart rate by ECG). The study concluded that the pharmacological activity of the stored solution was comparable to that of the fresh solution but that a new design for the Autoject was required [111].

Two injection devices were available commercially at the time: the combopen and the Astra injector. These two devices were compared in 1979 and 1980 in studies summarised below.

- The combopen was assessed in a study featuring 29 Servicemen and 4 Servicewomen [112]. Combopens containing atropine and P₂S stored at room temperature for a long period were compared to fresh solutions of atropine and P₂S and found to be similar in their effect on the subjects. Some of the subjects experienced slight unsteadiness and giddiness but no ECG abnormalities were observed and the all the combopens used fired satisfactorily.
- In December 1979 seventeen men at Swinton Barracks in Perham Down took part in tests to determine whether the combopen could be used by men wearing protective clothing [113]. The men completed an assault course wearing protective clothing and, on the shout of "gas", donned their respirators and injected themselves with a combopen. None of the men had used a self-injection device before. All reported some discomfort or pain after the injection but none considered the injection had seriously affected them. The study concluded that the combopen was suitable even in the hands of inexperienced men.
- The Astra injector was tested with 15 men [114], again comparing stored and fresh mixtures. The injections were given into the thigh through pads of material representing the layers of normal service dress and protective clothing. In one man, the Astra injector did not induce the expected levels of atropine and P₂S in the body and it was thought that the injector may have met resistance within the pad of material and emptied its contents before the needle had penetrated the leg. Otherwise, no difference was found between stored and fresh solutions and, generally, the Astra fired satisfactorily.
- In March 1980 the Astra injector and the combopen were compared in a trial at Battlesbury Barracks in Warminster [115]. Thirty four men completed an assault course and then injected themselves with either the Astra or the combopen before completing a second circuit of the assault course. Neither injector seemed superior to the other. The Astra injector was smaller (containing 1.4 ml of solution) which meant that the concentration of atropine and P₂S was higher. Despite this there was no difference in the discomfort experienced by the men after injections.

The combopen was selected to replace the Autoject and was used in the studies carried out to assess the new immediate treatment of atropine, P₂S and diazepam (often referred to as "triple therapy") after a course of pyridostigmine. These studies are described in the next section. One is most relevant here as it specifically considered how easy the combopen was to use [116]. Thirty seven volunteers took part, each taking at least 11 doses of 30 mg of pyridostigmine every 8 hours and then injecting themselves with a combopen while wearing protective gloves and inner liners (the gear they would be expected to wear in a chemical warfare environment). Two men went pale and started sweating after the injection but remained in that state for only 2 minutes. A third fainted immediately after using the combopen but recovered in 5 minutes. These cases were thought to have been induced by a reaction to any injection rather than the drugs used in the combopen. Overall, the study concluded that the combopen was easy to use and functioned satisfactorily [116].

19.4.4. Combined pyridostigmine and triple therapy studies

Having developed and tested the new (triple) therapy of atropine, P₂S and diazepam and having found a better injection device than the Autoject, the next series of studies considered the effect of prophylactic pyridostigmine and the triple therapy together. Triple therapy with either a 10 mg or a 5 mg oral dose of diazepam was considered. Over the period from 1979 to 1981 twenty six volunteers took pyridostigmine, in the dosing regime of 30 mg every 8 hours, over 1-5 days and then took the new triple therapy [92]. This work was preceded by a pilot study in June and July 1979 [117] in which 2 Servicemen and 2 Servicewomen took part.

The effect of pyridostigmine and triple therapy in exercising men was explored during the winter of 1979 [108]. Ten men took part [108], taking pyridostigmine over 5 weeks and exercising daily on a bicycle ergometer for 10 mins in a warm environment in the climatic

chamber while wearing full protective clothing. After this period, triple therapy was administered [93, 108].

These studies went satisfactorily and work then was conducted with volunteers at Bulford Camp in the winter of 1980 [95]. The men who participated took pyridostigmine for 21 days and on the 22nd day carried out an exercise (while wearing normal protective clothing) after which they gave themselves the triple therapy (a combopen containing atropine and P₂S, and a 5 mg tablet of diazepam) [96]. No untoward effects were observed. Similar trials were carried out by some of the men involved in testing pyridostigmine while undergoing normal duties at their home bases at Aldershot, Collingwood and Borden. They ended their tests by injecting themselves with triple therapy (as mentioned in Table 19) [89].

The next study of pyridostigmine and triple therapy with diazepam included an exposure to GB of 5 mg.min/m³ and was conducted in 1980 and 1981 [109, 118]. Thirteen men took part [109, 118] taking pyridostigmine over at least 5 days [92]. Ten of the men were then exposed to GB and immediately afterwards received triple therapy, while the other three were "given a dummy exposure to GB" [92] and served as controls.

These studies completed the work on the new triple therapy and pyridostigmine before that form of treatment was accepted by the Services in August 1980. Attention then turned to modifying the triple therapy by replacing the tablet of diazepam with a form of diazepam which could be given IM in the same injection as atropine and P₂S. The form of diazepam considered was a drug solution obtained from commercial sources referred to in Porton documents as the diazepam "Pro-Drug" TL4914. This solution, which could be administered by IM injection, was converted to diazepam in the body.

19.5. The incorporation of TL4914 in triple therapy

19.5.1. Introduction

The availability of TL4914 came to Porton's notice in 1980 and was discussed by COSHE in December of that year [119]. TL4914 was compatible with atropine and could be given in the same IM injection. The commercial manufacturer had completed some human studies with TL4914 but COSHE thought Porton would need to extend these to determine the acceptability of TL4914 to man, when given with atropine and P₂S [119].

The MC was consulted and, in May 1981 [120], concluded that enough information was available on TL4914 for Porton to start human studies. The MC recommended that initial studies should determine the maximum TL4914 concentration in blood that could be achieved without inducing sedation [120].

Human studies with TL4914 from 1981 to 1983 considered the dose levels, often comparing the effects of different TL4914 doses with doses of diazepam¹⁰. Studies from 1984 to 1987 explored the effect of replacing diazepam with TL4914 in triple therapy with and without a preceding course of pyridostigmine. These studies are described in the next three sections.

19.5.2. TL4914 human studies 1981 - 1983

Following the recommendation of the MC, the first two studies with TL4914 sought to identify the dose of TL4914 which gave the highest concentration in blood without any undue side-effects. The studies involved staff at the Royal Navy Hospital (RNH) Haslar and the Queen Elizabeth Military Hospital (QEMH) Woolwich [121]. IM and IV doses of TL4914 were to be given. In September 1981 COSHE expected that 12 doctors and nurses from the RNH Haslar staff and 12 volunteers from the military depot at QEMH Woolwich would volunteer to take part. The volunteers from Woolwich and Haslar were regarded by Porton as Porton

¹⁰ TL4914 was a solution which released diazepam into the body, but the amount of diazepam released was not necessarily the same as the amount of TL4914 ingested as a solution. Thus, a 10 mg dose of TL4914 was not the same as a 10 mg tablet of diazepam. Thus, the need to equate doses of TL4914 with doses of diazepam tablets.

volunteers: their details were to be recorded in the experimental records and they would be paid [121]. These studies had begun by November 1981 [122] but no mention of the work at RNH Haslar appears in the experimental records.

The work with volunteers at QEMH Woolwich appears to have been paralleled by similar studies at Porton. Experimental records covering 1981 to 1982 [118, 123] cite 25 men being involved in this work which saw men receiving 14 mg of TL4914 by IM injection and, three days later, another administration of TL4914 of 21 mg IM, or 28 mg IM, or 14 mg IV. Some of the entries in the experimental records pertaining to these 25 men are annotated with QEMH Woolwich. The remaining 18 men were studied entirely at Porton [123] and a report was produced of the results from these men [125] which concluded that 14 mg dose of TL4914 was found to be equivalent to a 5 mg dose of diazepam, judging from the effect TL4914 had on heart rates and the concentration of diazepam found in the blood.

Another study, conducted in 1983 [126], saw 15 men receive, over several days, TL4914 doses of 14 mg IV, 14 mg IM, 21 mg IM and 28 mg IM. The men fasted on the mornings when they received a TL4914 dose and lay on beds after the dose was given [127]. The study concluded that doses of TL4914 greater than 14 mg would be likely to cause levels of sedation and blurring of vision which would make them unsuitable for inclusion in triple therapy [127].

The effect of TL4914 on psychomotor and cognitive performance was explored in a study running from February 1982 to January 1983 [123, 126]. Doses of 15 mg and 30 mg of TL4914 were studied, with an oral dose of 5 mg of diazepam for comparison. Twelve men took part, each receiving these three doses on separate days with one week intervals between dose days [128]. Little real difference was found in the degradation of performance between an IM dose of 15 mg of TL4914 and an oral dose of 5 mg of diazepam. This equivalence, found in the other TL4914 studies outlined above, prompted work to start in 1984 with a modified triple therapy containing 15 mg TL4914.

19.5.3. Human studies with the new triple therapy

Initially human studies considered a new triple therapy with 15 mg of TL4914 incorporated into the combopen solution with atropine and P₂S, instead of a 5 mg tablet of diazepam. Studies explored the effect of this new triple therapy with and without a preceding regime of pyridostigmine tablets. Those studies were carried out mainly in 1984 with a few cases in them extending into 1985. Three types of studies were conducted.

The first study assessed the impact of TL4914 on the absorption of atropine and P₂S following a combined injection [129]. Twelve men took part in the study each taking pyridostigmine over 9 days. Two days into the pyridostigmine regime each man was given an IM injection of the new triple therapy. At the end of the pyridostigmine regime each man was given two IM injections of the new triple therapy separated by 15 minutes (as would be the practice in the field following exposure to nerve agents) [129]. The study drew the two conclusions given below [129].

- The absorption of atropine and P₂S was not affected by the inclusion of TL4914; in fact, absorption was quicker and attained higher concentrations.
- Two injections of the triple therapy resulted in the appearance of adverse effects; men were much more tired than after the single injection and some subjects became sufficiently sedated as to be difficult to rouse. The report suggested that the significance of these effects should be explored in additional studies.

The second study started in June 1984 testing the "safety and efficiency" of the new triple therapy for military acceptance and product licensing testing [130]. Studies were carried out in 1984, continuing into 1985, and involved the volunteers taking a regime of pyridostigmine tablets followed by an injection of the new triple therapy [131]. Sixteen men took part in these safety tests [131].

The third study followed on from the suggestion in the first study in assessing the effect of the new triple therapy on psychomotor and cognitive performance [132]. It compared the new triple therapy with the old one (with the 5 mg tablet of diazepam). Twelve volunteers took part each receiving a single injection of both forms of triple therapy over the course of two weeks. The study concluded that the new triple therapy caused a much greater impairment in performance than the old one and recommended that the dose of TL4914 to be incorporated in the combopen with atropine and P₂S should be reduced from 15 mg to 10 mg [132].

19.5.4. Human studies with the revised triple therapy

COSHE accepted in December 1984 [133] the conclusions of the third study and started a series of studies to explore the effects of reducing the TL4914 dose to 10 mg. The finding of the third study was explored in work carried out in 1985 which saw men taking a course of pyridostigmine before being given an injection of triple therapy. Twenty men took part: 10 being given an injection of triple therapy containing 15 mg of TL4914 and 10 an injection of triple therapy with 10 mg of TL4914. Their performance in psychomotor and cognitive tasks was assessed and the study confirmed that the dose of TL4914 should be reduced to 10 mg [134].

A comparison of the revised triple therapy, containing 10 mg of TL4914, was made with the old triple therapy (with a 5 mg tablet of diazepam) in a study running from late 1984 into 1985. Fifteen volunteers took part each receiving the old and the revised triple therapy over a two week period [135]. The effects induced by the revised triple therapy were similar to the old triple therapy and much less than the effects caused by triple therapy with 15 mg TL4914. Twelve other volunteers took part in a study in 1985 of the effect of the revised triple therapy on cognitive and psychomotor performance [136].

Studies in 1985 and 1986 considered the effects of taking two doses of the revised triple therapy, as outlined below.

- In 1985-1986 fifteen volunteers participated in a study in which they took a regime of pyridostigmine during which, in the first week, they received one injection of the revised triple therapy and, in the second week, two injections separated by 15 minutes [137]. This was a repeat of the first study carried out in 1984 (see Section 19.5.3). No significant systemic or local effects were seen after two injections of the revised triple therapy [137].
- The second study, in 1986, investigated the effect on psychomotor and cognitive performance of two injections (again, separated by 15 minutes) of the new triple therapy [138]. The report of the work [138] cites results from 8 volunteers but 10 volunteers are annotated as having taken part in the study in the experimental records [136]. The report notes that some men who took part were too sedated after two injections even to undertake the performance tests; it is possible therefore that the 8 men cited by the report are those who did actually take part. The impairment in performance after two injections of the revised triple therapy lasted from 15 minutes to 4.5 hours [138].

Other studies were conducted to determine whether the revised triple therapy was acceptable when men were wearing full chemical warfare protective clothing. Fifteen volunteers exercised in protective clothing and then administered a single injection of the revised triple therapy in a study in 1985 [139]. The physiological and psychological effects of the combination of wearing protective clothing and an injection of the revised triple therapy [140] were investigated in 14 volunteers in 1986 and 1987 [136].

The MC reviewed the work with the revised triple therapy in November 1988 [141]. It concluded that including 10 mg of TL4914 in a combined injection with atropine and P₂S produced higher concentrations of the drugs in the body, in a shorter time, than taking a 5 mg tablet of diazepam with atropine and P₂S. The MC concluded that the studies with the revised triple therapy suggested no increase of sedation or behaviour disturbance over that found in work with the old triple therapy (with the tablet of diazepam) [141].

19.6. New prophylactics: physostigmine and hyoscine.

19.6.1. Human studies with physostigmine 1982 - 1987.

Animal work in 1970 had shown that physostigmine given as a prophylactic protected animals from poisoning by GD and GA and was compatible with an immediate treatment of atropine and P₂S (which increased the protection afforded by physostigmine) [142]. Subsequent animal work in the 1970s confirmed the protective effect of physostigmine but, at the time, "the safety factor for physostigmine is considered to be too low for it to be considered for development as a field treatment in man" [72]. It was from this work that the studies into pyridostigmine originated.

Physostigmine was revisited in the early 1980s. Like pyridostigmine it is a reversible inhibitor of ChE but was found to be more effective in animals than pyridostigmine against the changes induced in the central nervous system by nerve agents [143]. Animal studies suggested that a dose of physostigmine sufficient to inhibit ChE by 20-40% would be most beneficial in protecting ChE from attack by nerve agents [143] and human studies sought to identify the dose of physostigmine which would achieve this in man.

In approving the first human study COSHE noted that physostigmine had "revolutionised" the treatment of myasthenia gravis and that the open literature referred to cases in which it had been used, in doses of 0.5 mg every 1-2 hours, to treat cases of poisoning from some anti-depressants and phenothiazines [143]. A professor at Oxford University was consulted over the design of the study [144], which subsequently was conducted in 1982 using IV infusions over 10 minutes of physostigmine in doses increasing from 0.1 mg to 0.8 mg [143]. Eighteen volunteers took part: 12 men received three IV infusions and 6 men received two IV infusions in this dose range. Doses were given at least 3 days apart. The conclusions drawn by the study were [143]:

- the maximum RBC ChE inhibition, which occurred after the largest dose of 0.8 mg, was 39%;
- no serious symptoms were observed although one man became dizzy and nauseous after his 0.8 mg IV infusion;
- physostigmine disappeared from the blood quite quickly so, if the drug was to be used as a prophylactic, a formulation offering sustained delivery was required.

Further studies in 1983 assessed IV infusions over longer periods to identify the effects associated with the sustained delivery of physostigmine. Thirteen men received 1.4 mg by IV infusion over the course of an hour (0.6 mg in the first 30 minutes and 0.8 mg in the second half-hour) [145, 146]. The observations made are listed below [146].

- Blood ChE inhibitions of up to 45.4% were obtained and were accompanied by a slight increase in heart rate. However, no changes in blood pressure or clinically significant changes in a variety of haematological and biochemical features were observed.
- Side effects associated with cholinergic stimulation were seen in some subjects but these cleared after the end of the infusion. One man experienced "severe adverse effects" (sweating, weakness in the legs, tingling in the arms and hands and abdominal cramps) although these effects were reversed by atropine and he made a rapid recovery.

Other studies started in 1983 and continuing into 1984 [147, 148] considered the effect of a sustained delivery of physostigmine on memory and information processing. They used IV infusions of physostigmine but at a lower dose of 1.1 mg over 70 minutes (0.5 mg being given in the first 10 minutes and 0.6 mg over the next hour). The results of these studies are

outlined in a later section in this chapter which brings together all the studies carried out into the effect of nerve agent treatments on memory.

The next study in 1984 also used a lower IV infusion dose than 1.4 mg over one hour. The study sought to compare the pharmacological activity of physostigmine given by IV infusion and orally. This study, the forerunner of an investigation into the design of tablets to release physostigmine, infused 1.8 mg over about 2 hours (0.6 mg in 2 minutes followed by 0.6 mg hourly for the next two hours) [131]. Three volunteers took part in this study and each received, on a different day, an oral dose of physostigmine of 2 mg [131].

An investigation into the design of physostigmine tablets began in November 1985 [140] and continued into 1986 [131, 149]. Initially the pharmacological activity of 2 mg rapid release physostigmine tablets taken by volunteers in the first week was compared with the activity associated with 9 mg, 12 mg and 15 mg slow release tablets taken in the next three weeks respectively [150]. The investigation was dogged by problems with the formulation of the slow release tablets: various formulations intended to deliver physostigmine over 12 hours were tried but found to deliver too much in the first 6 hours [152]. Overall 18 volunteers took part in the investigation [131, 149].

The investigation was extended in 1986 and into 1987. New formulations of 12 mg and 15 mg of physostigmine were assessed but this time compared to an IV infusion of 0.6 mg over 10 minutes instead of the 2 mg rapid release tablet [149, 152]. Fourteen volunteers took part in this extension.

19.6.2. Human studies with hyoscine 1986 -1989.

Investigations with hyoscine seem to have their origin in the search for a means of administering physostigmine [153]. COSHE noted in April 1983 [154] that adhesive patches placed on the skin were used to treat seasickness by the transdermal administration of hyoscine. The first concern was whether commercially available patches would adhere to the skin for 24 hours while the wearer was engaged on military duties. Studies in 1983 and 1984 investigated this using commercial patches containing a placebo.

- The first study involved 48 volunteers wearing patches on the chest, forehead, temple and behind the ears [155]. Forty six of the volunteers wore 8 patches (one on the left and one on the right at each of the four sites), the remaining 2 wore 4 patches, either on right-side or left-side sites [155]. This study included a trial conducted at the DNBCC Winterbourne Gunner [156] involving other volunteers drawn from the ranks of those attending courses there.
- The second study explored if patches would remain in place in hot climates; twenty five volunteers from a detachment of the Royal Corps of Signals stationed in Kenya participated [153]. Each man had a small patch, containing a placebo, stuck behind each ear. One was patch was placed on dry skin and the other placed on skin previously swabbed with alcohol. The patches remained in place for 24 hours and the swabbing with alcohol was found not to improve adhesion [153].

In parallel with these studies, animal work was commenced to explore the effect hyoscine had in treating nerve agent poisoning. The work showed that hyoscine protected guinea pigs from GD poisoning [157] and that the combination of physostigmine and hyoscine, given as a prophylactic, was effective against GA, GB, GD and VX [157,158]. The toxicity of the combination of physostigmine and hyoscine was investigated in animals [159]. COSHE considered these results in April 1986 [151] and human studies with hyoscine began.

An outline of the studies is given below:

- in 1986 and 1987 eight volunteers received 0.6 mg of hyoscine in capsules, by IM injection and IV infusion [149];

- in 1987 ten volunteers received 0.6 mg of hyoscine by IM injection and 0.6 mg of physostigmine by IV infusion (separately and together) [149];
- in 1987 and 1988 eighteen volunteers received 0.6 mg of hyoscine by IM injection into the thigh [136, 160] and, in 1988, another eight volunteers had an IM injection into the thigh of 0.4 mg of hyoscine [136];
- in 1989 seventeen volunteers had a hyoscine transdermal patch placed behind an ear or on the forearm [136], the patches containing 1.5 mg of hyoscine delivered at a rate of 5 µg per hour over 72 hours [141].

These studies complete the work conducted with hyoscine, either alone or with physostigmine, during the period covered by the survey. Further studies with both hyoscine and physostigmine continued into the 1990s.

19.7. Other studies with nerve agent treatments

19.7.1. Car Driving

The effect of nerve agent treatments on performance was commonly assessed by asking volunteers to undertake psychomotor and cognitive tasks. In the 1970s Porton sought to study performance more realistically and car driving was chosen. At that time, manoeuvring and gap-judging were widely used to study the effects of a variety of medicines (including atropine, Valium and clobazam) [161].

A series of studies were conducted involving volunteers driving a Porton car, usually a Ford Escort, after taking a nerve agent treatment. These driving studies took place on a traffic-free private road system [161]. The studies started in the late 1970s and continued into the 1980s; volunteer WRAC drivers helped in 1974 to calibrate the instrumented car used in these studies.

Almost all the nerve agent treatments covered in this chapter were tested in driving studies. Men taking a regime of pyridostigmine tablets over the course of a week took part in driving trials in which three types of test were considered. For each of the three, 16 men participated with half taking placebo tablets and therefore serving as controls [161]. The types of test are outlined below.

- Manoeuvring and gap-judging in daylight and darkness.
- Car-following and perceptual load. Here the volunteers were asked to follow a lead car (a Vauxhall Viva) driven by a member of Porton staff. The distance between the cars was measured. To examine perceptual load volunteers, who were fitted with a throat mike, were asked to say "car" every second. Their recitation was paced by a metronome.
- Navigation from memory. Volunteers were taken to a position in the road system and then presented with a route, either as a map or as a series of verbal instructions. The presentation of this information was repeated until the route had been learned. The volunteer was then told how his present position related to the route (whether it was at the top or bottom of the map, or whether it represented the start or end of the route as conveyed by the verbal instructions). The volunteer then drove until they believed they had reached their destination or until they confessed they were lost.

The work concluded that no evidence had been obtained from the driving studies to suggest pyridostigmine would present a hazard to drivers [161]. The effects of atropine on driver behaviour were studied [162]. Here the aim was to assess confidence and the willingness to act when driving through gaps. Ten volunteers took part, each performing the driving tests after an IM injection of 2 mg of atropine and, one week later, repeating the tests after an IM

injection of saline. The tests, carried out in the afternoon and in the evening after dark, are outlined below.

- Gap-driving skill. The men were presented with a series of five gaps which were at least as wide as the car they were driving, a gap exactly the width of the car and gaps with clearances from 1.25 cm to 5 cm. Their skill in driving through these gaps was recorded.
- Confidence. This was measured as the width of the gaps through which the men said they could drive. They were presented with six gaps, three of which were narrower than the car (the men were warned that some gaps may be so), and asked which ones they would be prepared to drive through.
- Willingness to act. Here the volunteer set the dimension of the gap himself, by instructing a member of Porton staff to adjust a gap presented to him initially to the narrowest they considered possible. The volunteer then attempted to drive through the gap.

Atropine had no effect on the skill of the men in negotiating the gaps but reduced their confidence and willingness to act by inducing more cautious behaviour [162]. It was difficult to know what to make of this: most men acknowledged that if they had been driving their own car between buildings or other vehicles they would have been even more cautious (so they had been a little more reckless in the test than they would have been in real life). On the other hand, all the men were concerned they should not appear to be bad drivers which made them drive more cautiously than normal [162].

The effect of atropine on car-following and perceptual workload was also studied [163] in tests similar to those used in the pyridostigmine study. Separate tests were conducted with the lead car travelling at 20 mph and 30 mph. The work concluded that atropine appeared to induce safer driving behaviour, probably because the volunteers who took part recognised the effects of the drug [163].

Similar driving studies were conducted after men had taken an oral dose of 10mg of diazepam [109, 118] in 1980 and 1981, and after men had been given a single IM injection triple therapy with either 10 mg or 15 mg of TL4914 [131,136] in 1984 and 1985. The effect of transdermal hyoscine on driving behaviour was set to be studied [164, 165] after the end of the period covered by the survey.

19.7.2. Memory tests

Memory tests were not normally included in studies at Porton as they were too protracted and liable to "confound other tests of mental function" [166]. But, by the late 1970s, various open literature reports had shown that memory was impaired by benzodiazepines [166]. Therefore a series of studies was carried out to assess the effect of atropine and diazepam (separately) on memory. Twenty two volunteers took part: 10 receiving 2 mg of atropine IM, 6 taking a 2 mg oral dose of atropine, and 6 taking an oral dose of 10 mg diazepam. In each case the men performed the memory tests twice, once after these doses and again, generally a few days later, after a placebo dose [166].

The tests, which sought to distinguish between the storage of information in memory and the retrieval of it from memory, are outlined below.

- The digit span test. A sequence of random digits was read to the volunteer at a rate of one per second. At the end of the sequence the volunteer was asked to write down the numbers he had heard. The process was repeated with the length of the sequence of numbers (different ones between sequences) increased by one. The volunteer's performance was judged by the longest sequence he could remember accurately at the first attempt and at the second attempt (if the volunteer failed he was given another sequence of the same length).

- Associative memory. A list of 10 pairs of words was given to the volunteer. After memorising them the first of a pair (selected at random) was read to him and the volunteer had to respond with the second word in the pair. The test was conducted with two lists of 10 pairs. At the end, the volunteer was asked to recall any of the 20 words on the list. The timing of the test allowed a distinction to be drawn between the effect on storage and retrieval. Volunteers were given one list of 10 pairs before dosing and asked to recall information before and after dosing. The second list of pairs was given after dosing, so the volunteer had to store and retrieve the information while under the effects of the treatment [166].

The study concluded that atropine and diazepam impaired the ability to store information in memory, while atropine also impaired the ability of the memory to deal with numerical information [166]. Similar memory tests were conducted with TL4914, involving 10 men receiving an IM dose of 10 mg, 15 mg or 30 mg [123].

Studies exploring the effect of physostigmine on memory have already been mentioned. They were prompted partly by open literature reports that physostigmine improved memory [148], although this literature was confusing and equivocal [147]. Eighteen volunteers took part in one study in which they completed a battery of memory tests. Nine of the volunteers received an IV infusion of 1.1 mg over 70 minutes, the other 9 receiving a saline IV infusion and serving as controls [147]. The tests included the two mentioned previously but some others as well:

- volunteers were presented with a set of pictures, once during the IV infusion and again afterwards, and asked to recall what they showed (with various delays between seeing the pictures and being asked to recall them);
- long term recall was tested by asking volunteers to recite as many four-footed animals as possible;
- a list of 20 common objects was read to the volunteer, who then had to retrieve them from a box which held those 20 objects together with 20 other objects.

The study failed to demonstrate any clear memory effects [147]. The second study [148] featured 16 volunteers each of whom received the same dose of physostigmine by IV infusion as was used in the first study. Here the study tested detection and recognition and the ability to search the memory and make comparisons. The study used a Sinclair Spectrum computer, through which digits were presented in the centre of a TV screen at the rate of one per second. The volunteers responded (in various ways) to the digits by using the keyboard [148]. The study indicated that physostigmine improved detection and recognition.

19.7.3 Miscellaneous pyridostigmine studies

More studies were conducted with pyridostigmine after it had been accepted (and referred to as NAPS) by the Services in 1981. The first, which ran throughout 1982, investigated whether pyridostigmine induced muscle tremor. Open literature reports noted that a shorter acting carbamate, neostigmine, could cause degenerative changes to the rat's neuromuscular junction. Similar changes had been seen in patients suffering from myasthenia gravis who were treated with pyridostigmine although it was not clear if those changes were induced by the disease or the treatment [167]. If pyridostigmine had this effect it was felt likely that would be reflected in normal muscle tremor [167].

The study was carried out in conjunction with the MRC Hearing and Balance Unit and the National Hospital for Nervous Diseases. Muscle tremor in the hand and the index finger was measured following a double dose (60 mg) of pyridostigmine in 12 volunteers, and following the normal dosing regime (30 mg every 8 hours) over two weeks in another 12 volunteers. The study made the following points [167]:

- no statistically significant change in hand or finger tremor was found after the normal dosing regime of pyridostigmine;
- volunteers experienced the usual symptoms of stimulation induced by pyridostigmine inhibiting ChE (runny nose, sweating, cramps, tightness in the chest) but none were of clinical significance, all passed off quickly and were not sufficient to interfere with duties.

Another study in 1982 considered the effect of standard field rations on the absorption of pyridostigmine [168]. Traditionally in the Services standard field rations were associated with constipation. Twelve volunteers lived on field rations for 9 days while taking NAPS tablets and another 12 volunteers ate whatever they chose while taking NAPS. No significant difference in the absorption of pyridostigmine from NAPS tablets was found between the two groups and no untoward effects were experienced [168].

The interaction between pyridostigmine and surgical drugs available to military doctors was discussed by the MC in 1982 [169]. It was clear to the MC from open literature reports that this interaction could not be forecast with great accuracy and some human studies would be necessary. Of concern was the interaction between pyridostigmine and anaesthetics available to military doctors to relax muscles. Two types of studies were conducted to investigate this interaction.

- The first explored alcuronium in volunteers who had taken a course of pyridostigmine. The method used was to isolate the forearm, by using tourniquets, to prevent alcuronium entering the body's circulation. To guard against the possibility of the anaesthetic finding its way past these barriers, full resuscitation equipment was on hand for each test as were two senior specialist anaesthetists; volunteers were studied one at a time [170]. Twelve volunteers [171] took part in the study which ran over the latter half of 1983. The study was extended in 1984 to explore two other anaesthetics, vecuronium and D-tubocurarine. Four volunteers took part in this extension [171].
- The second type of study, exploring the interaction between pyridostigmine and another anaesthetic, suxamethonium, used a different technique. Here, the rate at which suxamethonium was destroyed in blood was used as an indication of the interaction [172]. Blood samples were taken from men taking pyridostigmine as part of another study and suxamethonium was introduced into the blood samples.

19.7.4. Pyridostigmine and SFEMG

SFEMG work with volunteers exposed to GB is outlined in the nerve agent chapter and relates to an exposure to GB of $15 \text{ mg}\cdot\text{min}/\text{m}^3$. Also mentioned is an SFEMG study of volunteers taking nerve agent treatments and then subjected to a lower exposure of GB of $5 \text{ mg}\cdot\text{min}/\text{m}^3$. This study featured pyridostigmine. Twenty four volunteers took part, split into four groups of 6 [173]:

- one group took pyridostigmine tablets over 5 days and then was exposed to GB of $5 \text{ mg}\cdot\text{min}/\text{m}^3$ ($t = 30$ minutes);
- one group took pyridostigmine tablets over 5 days and was not exposed to GB;
- the other two groups took placebo tablets, with one group then being exposed to GB.

The first two groups are of interest here. SFEMG measurements were taken 5 times in volunteers in these groups: before starting the pyridostigmine regime; after the first dose of pyridostigmine; after the five days of the regime; 3 hours after the GB exposure (or 3 hours after the regime ended in the group not exposed to GB) and 3 days after the GB exposure (or 3 days after the regime had ended). The conclusions drawn from this study were [173,174]:

- pyridostigmine caused no significant change in SFEMG readings;
- volunteers taking pyridostigmine did not display any change in SFEMG when subsequently exposed to GB (this was significant because the volunteers who were exposed to GB but took placebo tablets showed slight SFEMG changes).

The study was extended to explore the effect on SFEMG measurements of pyridostigmine and triple therapy (atropine, P2S and TL4914) [175]. Eight volunteers took part, each having four sessions of SFEMG measurements, with the triple therapy being taken between the last two sessions. The study concluded that no significant changes were observed in SFEMG measurements [175]. Another SFEMG study was conducted with 9 volunteers [176] taking part in an extension of the study investigating the interaction of pyridostigmine and alcuronium. All these SFEMG studies were reviewed in September 1989 [177] and it was concluded that no abnormality of SFEMG measurements had been seen in men taking NAPS tablets.

Chapter 20. Skin Protection

20.1. Clothing

20.1.1. Introduction

Clothing can protect the wearer from liquid agents and the vapour they give off. A distinction is drawn here between normal Service clothing and specially designed protective clothing, commonly referred to as Nuclear, Biological and Chemical (NBC) kit (or during World War II, "anti-gas" clothing) and usually worn over normal Service clothing. Studies with clothing during World War II fall into the following categories:

- the degree of protection given by normal Service clothing impregnated with substances;
- investigations into whether impregnated Service clothing and rubber mixes which might be used in anti-gas respirators irritated the skin.
- the protection afforded by anti-gas clothing and other forms of protection (gloves used in factories producing CW agents) against liquid agents and vapour;
- the efficiency of decontamination methods in ridding clothing of liquid and vapour.

Studies in the first three of these categories are discussed in this section of the chapter. Studies of decontamination methods are described in the final section of the chapter, as they include tests to investigate the effectiveness of decontaminating materials other than clothing (including items of equipment and foodstuffs).

Porton work before 1939 showed that fabrics impregnated with carbon conferred "resistance to the passage of H vapour" [1]. Work during World War II investigated different ways of impregnating normal Service clothing; carbon and powders were tried. Work was also conducted with dusting powders which could be applied underneath clothing (in a similar fashion to talcum powder). The protection afforded by these methods was assessed in human studies mostly with H vapour although a few involved liquid agents.

Studies during World War II investigated the effects on man of wearing impregnated clothing. Many of these studies involved volunteers wearing articles of impregnated clothing over a long period of time to find out if the clothing irritated the skin. Other studies saw small patches of impregnated clothing being fixed to the arms of volunteers and the skin reaction noted. This method was also used to investigate the irritancy of rubber mixes which were being considered for future respirator designs. In that context the method is referred to as the "patch test". Patch tests with rubber mixes began in 1940 and continued until the mid-1980s. Many thousands of volunteers took part but, as they did not involve agents or substances, they are not described in detail in the survey. Annex G gives an overview of patch tests of rubber mixes.

Hundreds of studies were carried out during World War II to investigate the degree to which existing protective clothing was penetrated by liquid and vapour. As material technology and science advanced in the post-war period more and more attention was paid to the design of protective clothing. Many human studies were conducted to determine whether material being considered for protective clothing prevented the penetration of H liquid. A few thousand volunteers took part in these studies. Work to investigate whether protective material prevented the penetration of G¹¹ and V agent liquid was conducted with devices in

¹¹ It should be noted that the study in 1951-1953 (described in the nerve agents chapter) in which liquid G agent was placed onto pieces of clothing attached to the forearm of volunteers was not an investigation into skin protection as such. It sought to find out the effect of G liquid when it landed on normal (unimpregnated) Service clothing compared to when it impacted directly on bare skin.

the laboratory, with animals and (as described in the nerve agent chapter) with resected human skin.

Similarly, the effectiveness of protective clothing in preventing the passage of vapour (from H, G and V agents) was carried out in laboratory studies with devices or animals. An early example of this work [2] used paper formulated to detect vapour, placed underneath protective clothing on to which H, VX and GF vapour was directed. Subsequently more elaborate laboratory techniques were developed.

20.1.2. Impregnated Service clothing

In 1939 denim outfits were being considered for mechanised units of the Army rather than the normal khaki Service dress [3]. Different ways of impregnating denim and, latterly, the protection given by impregnated denim suits were tested in wearing trials in late 1938 and early 1939 [4]. Observers wearing the suits were exposed to H vapour of 936 mg.min/m^3 ($t = 60 \text{ minutes}$)¹² daily for five successive days and continued to wear the suits throughout [3]. No burns were recorded. Three of the observers wore suits in which one sleeve was replaced with unimpregnated denim. They developed general reddening of the skin beneath the sleeve.

The denim suits were also tested with liquid agents. Four vesicants were used: H, L, a mixture of H and L, and HT. The drop sizes were of 2 mm diameter in each case with a further drop size of 3 mm diameter for HT. Nine men took part in the tests each having drops of all 4 vesicants placed on the denim suit they were wearing at one site (shoulder, thigh, forearm or upper arm). After the drops were applied the men continued to wear the suits for 6 hours. The study concluded that [3]:

- the impregnated denim suits gave good protection against H vapour;
- considerable, but not complete, protection was afforded against 2 mm drops of the four vesicants although the effect of L was erratic (in 7 cases it had no effect at all but in one case it produced a severe burn on the shoulder blade).

The method of testing impregnated clothing against H vapour was used in later studies and an exposure to H of around 1000 mg.min/m^3 was common although the length of the exposure varied. Other studies of this nature are summarised below.

- In 1941 a new method of impregnating clothing with carbon was developed and suits were worn by men at RAF and Army units and by civilians (workers in factories and personnel of the LMS Railway Company). After they had been worn the suits were tested to see if they still offered protection. Ten volunteers wearing the worn suits were exposed to H vapour in the same fashion as the previous study and continued to wear the suits [1].
- By 1942 a better method of impregnation had been developed [5]. Impregnated Army battledress suits and RAF suits were worn for 6 months by people at their own units. At the end 36 suits were tested by volunteers. They were subjected to the same exposure of H vapour as previously but at intervals of 48 hours. The number of exposures continued until a skin reaction was noted or until a man had been exposed 4 times [5].
- In August 1944 [6] volunteers tested impregnated clothing and again were exposed to H vapour of a nominal 1000 mg.min/m^3 but sometimes over 30 minutes as well as over 60 minutes. This study also saw men testing clothing against short and long exposures of H vapour. Here the exposures were in the range of $305\text{-}350 \text{ mg.min/m}^3$ over either 3.5 minutes or 90 minutes.

¹² The report of the work cites the exposure as parts per million, but this has been converted. The survey attempts to use only mg.min/m^3 as a means of expressing vapour exposures.

- In 1945 volunteers tested jungle clothing impregnated in converted mobile laundries (that would be suitable for field use) [7]. Eighteen men wearing a jungle jacket and trousers were exposed to H vapour (nominal 1000 mg.min/m³) in the tropical gas chamber. Previously they had warmed up in another chamber to induce sweating. Twelve of the 18 men repeated the work with other suits.
- Also in 1945 eighteen men tested jungle clothing impregnated by a new process [8]. Again the men warmed up and then, wearing impregnated jungle suits, were exposed to H vapour varying from 574-1024 mg.min/m³. Each man continued to wear the suits for 4 hours after the exposure. Each man underwent two exposures.

Two studies were slightly different to these. The first, in 1939, tested the protection given by impregnated socks [9]. Three types of impregnation were assessed and the study was split into two parts as outlined below.

- Twelve men participated in the first part: each had one forearm exposed to H vapour (for 40, 60 or 75 minutes) while wearing a piece of sock. Each man underwent this process three times (once for each type of impregnated sock).
- Fifteen men participated in the second part: they wore socks for 4 days. Afterwards a 3 mm drop of H was placed at the base of the big toe on the new Army ankle boot (which was worn over the sock). After the boots were contaminated the men continued to wear them for 6 hours, removing them on going to bed. The next morning the boots were put on again and worn for another 12 hours. One man, who showed a burn on one foot 2 hours after the application of H to one of his boots, did not continue the following morning.
- The second part was extended: seven men wore boots which had been contaminated with H liquid (in the same way as before) over ordinary socks for 6 hours. A further 3 men wore, for 3.5 hours, boots which had been contaminated in the same way but were then left in a closed shed for 14 days.

The second study investigated the means of tackling a particular problem caused by H vapour. The report of the work, written in 1942 [10], explains that the "extreme vulnerability of the scrotal region, compared with other parts of the body, has been recognised since the last war. Casualties occur due to scrotal burns under conditions where discomfort only is sustained in other parts of the body". In 1942 an ointment, referred to as AG (Anti-gas) No. 3, was available and protected the neck from the effects of H vapour. Thus, if a man used AG No. 3 and wore a respirator, scrotal injuries would be the main cause of casualties. AG No. 3 was not a suitable protection for the scrotal region as it got rubbed and sweated off.

The study began in March 1942 by exploring "the full extent of the danger" [10] from H vapour to the scrotal area.

- Six volunteers wearing ordinary battledress (shirt and shorts) and protected by service respirators were exposed to H vapour of 31.2 mg/m³ for one hour (1872 mg.min/m³). The men wore the same clothing for the rest of the day which was spent mostly in the open air, and slept in the same shirts.
- All had some redness to the trunk, arms, neck and thighs and "burns varying from severe erythema to vesication of the scrotum and the penis occurred in each case" [10].
- "The scrotal injuries alone were of casualty severity, as burns on other parts of the body, although irritating were relatively mild and would not have prevented the men from carrying out military duties". Following this test the six men were unfit for duty for 7, 10, 10, 28, 28 and 28 days (respectively).

Impregnating underwear with AV (Anti-Verm) powder had been tried in 1930 as a means of protecting the scrotal region from H vapour [10] but sweating destroyed the protection. In 1942 a new method of impregnating underwear with AV had been discovered: garments were squeezed and pounded in a bath of AV powder in water and then wrung out and allowed to dry. This process was repeated many times.

The next phase of the study assessed the protection given by undergarments impregnated with AV by this method. First, various Service undergarments were tested (the knickers issued to the WAAF and ATS, the pantees¹³ for the ATS and Army pants) to find out which held the AV the best. The closely knit WAAF knickers proved most effective with ATS pantees a close second. These were subjected to wearing trials and, afterwards, tests against H vapour. At the time no comparison had been made between AV impregnated clothing and carbon impregnated clothing, so undergarments of both were included in the wearing trials.

- Of greatest concern in 1942 was the need to protect soldiers operating in tropical conditions from the effects of H vapour and therefore wearers who habitually perspired freely were needed for the wearing trial. A leading industrialist allowed Porton to conduct wearing trials with 22 workers in a melting shop at a steel factory in Sheffield. The workers wore ATS pantees for 32 hours.
- After this trial 4 of the pantees (and two impregnated pantees that had not been worn) were tested against H vapour in the normal way. Six Service volunteers, wearing the pantees were exposed to H vapour for an hour on 4 occasions. The men continued to wear the pantees for 10 hours after each exposure.

No skin effect of any kind was found in the area protected by the pantees. The study concluded [10] that both carbon and AV impregnated pantees afforded a high degree of protection against H vapour. However, it was widely known that maintaining the protective value of carbon impregnated clothing in the field was difficult [10].

Maintaining the AV impregnation meant that undergarments had to be re-treated periodically [11] so attention turned in 1943 to dusting underpants with AV powder. Two wearing trials were conducted [11].

- The first involved workers at a steelworks in Rotherham wearing ATS pantees during four 8-hour shifts. In tests of the pantees with volunteers at Porton against H vapour (in the usual manner) it was found that a satisfactory degree of protection was retained. This was significant because the conditions in the steelworks were very hot, particularly at night under blackout conditions.
- The second trial saw RAF personnel wearing WAAF pantees during summer weather. The wearers applied the AV dusting powder themselves every 72 hours. A tenth of the men complained of irritation in the early stages of wearing but generally this did not persist (although in one man the irritation was so severe that on medical advice he stopped wearing the pantees). Tests of the pantees with volunteers at Porton against H vapour proved inconclusive.

The main problem encountered in this part of the study was that sweat deactivated the AV powder. Almost 80% of the powder was lost in the RAF trial during a half hour strenuous exercise [11].

The study [11] resumed in the early 1950s after the General Staff issued a requirement for anti-gas clothing to protect against H vapour which did not need to be re-impregnated. Dusting powders were again studied but with various techniques used to wash and bleach underwear so that it retained the powder. Charcoal impregnated undergarments were also investigated. Several wearing trials to test for irritancy were carried out during the period

¹³ This is the spelling used in contemporary reports, rather than the more expected "panties".

1951 to 1953 involving over 350 volunteers. Some wore undergarments while going over the assault course and boot track at Chatham.

The study culminated with two field trials at Porton in August 1953 [11] in which volunteers, wearing either AV dusted undergarments or charcoal-impregnated undergarments, were exposed to H vapour. Before exposure the men wore the underwear for 3 days, day and night, without bathing. For the exposure, the men were "suitably protected above the waist" [11], wearing an impregnated vest, impregnated denim blouse, impregnated muffler and a respirator, with their hands, wrists and neck inuncted with AG ointment. The two trials were as follows.

- In the first trial a patch of ground was sprayed with H liquid by special watering cans. The men were exposed to the vapour given off by the liquid for 2.5 hours (giving an overall exposure of 800 mg.min/m³ [11]). The men were engaged in light digging during the exposure.
- In the second trial six further volunteers and four from the first trial underwent a similar procedure but with twice as much liquid H being sprayed on the ground (resulting in an overall exposure of 1700 mg.min/m³ [11]). The men who had taken part in the first trial were removed when their total exposure from both trials had reached 1700 mg.min/m³.

In only one instance was there any indication of skin damage within the area protected by the undergarments. Charcoal impregnation and AV dusting were equally effective but in the field AV dusting would probably be preferred [11]. This concluded the study on finding the means to protect the scrotal region from H vapour.

The method of impregnating clothing with AV, tested in the pantee trials in 1943, was used during World War II to impregnate entire suits of battledress with AV [12]. Experience in 1944 suggested that AV impregnated clothing worn in tropical conditions could cause serious toxic effects: the men who wore such clothing being subjectively affected with the commonest signs of cyanosis and methaemoglobinaemia¹⁴ [12]. Thirty nine volunteers took part in wearing trials at Porton in which they wore suits impregnated with AV continuously for several days, and on each day spent 3-7 hours in the climatic room under various conditions (hot/humid, warm/humid, warm/dry, normal). Twelve other volunteers wore suits impregnated with one of two other powders (CC2 or impregnite B). Before entering the room, and upon leaving it, blood samples were taken from the men for analysis. The study confirmed that wearing AV impregnated suits in hot and humid conditions would cause methaemoglobinaemia but that the effects wore off quickly once the clothing was removed [12].

20.1.3. Protective clothing.

During World War II many hundreds of tests were conducted to assess the protection given against CW agents by protective garments. The majority of the volunteers who reported to Porton during World War II took part in these studies. No volunteer whose skin was found to be sensitive to H by the H sensitivity test was permitted to take part in these studies. The studies considered all manner of protective clothing which was then in use: Service anti-gas gear (such as capes, rubber overboots, respirator facepieces, and gloves), civilian protective clothing (such as the suits issued to ARP wardens, and oilskin capes and jackets) and industrial clothing worn by people in factories producing CW agents (largely different types of gloves). Tests were also conducted on captured enemy Service protective clothing and garments used by Russian and French allies [14, 15, 16, 17, 18, 19, 20, 21, 22].

These tests during the war predominantly involved H liquid although some used liquid L and liquid HN-1, HN-2 and HN-3. The tests were conducted in two ways, as outlined below.

¹⁴ With cyanosis the skin takes on a bluish tinge induced by a lack of oxygen in the blood. Methaemoglobinaemia is a shortage of the oxygen-carrying protein present in red blood cells.

- Drops of liquid were placed on the garment while it was being worn by a volunteer. Often only one drop was used but sometimes a few were placed over a small area. This form of study was similar to the one recounted with impregnated socks, in which a drop of H was placed on a boot worn by the volunteer and the effects on the foot noted.
- The majority of liquid tests with clothing worn by volunteers involved liquid being placed on the clothes on the arm region (in the case of gloves being worn by a volunteer, a drop was usually placed either on the finger, the palm or the back of the hand). Some studies saw drops being placed on clothing on the shoulder region, the upper chest or the upper back.
- Small pieces were cut from the protective garment being investigated and attached to the arm of a volunteer. A drop of liquid agent would then be placed onto the piece of material and left for a few hours.

The second form of test became more common during World War II, and was adopted as the standard in studies of H penetration after World War II. The other form of test carried out during World War II considered the penetration of vapour through protective clothing. Here the method used in the impregnated sock study was used: a piece of material would be attached to the arm and vapour would be passed onto the material through a tube for a few minutes. Very rarely were these vapour tests conducted while the volunteer was wearing the garment (one exception is given below). H vapour was usually used, but sometimes vapour of other compounds, such as L, was employed.

Almost all the assessments of the penetration of vapour featured protective clothing. However, three studies are recorded in which normal (and unimpregnated) dress was used. These are outlined below, the second two being conducted in the way vapour tests with protective clothing had been.

- In 1939 ten volunteers took part in a study of the protection afforded by Service kilts [13]. Five men wore kilts and were exposed, while wearing respiratory protection, to H vapour of a concentration of 1 in 500,000 for an hour on each of 5 successive days. Five other volunteers wore kilts exposed in this way for an hour on each of two days.
- In 1939 eleven volunteers took part in a study to assess the protection afforded by standard serge material against L vapour [13]. Three pieces of serge were fixed to their arms and L vapour was directed onto each piece through a tube for 60 minutes.
- The final study was not concerned with assessing protection but provides the third example of normal unimpregnated Service dress being used in vapour studies. During World War II detector papers were available which were formulated to change colour when vapour from chemical warfare agents came into contact with them.
 - Typically the papers were laid on an article of clothing to check that it had been decontaminated properly [24]. Different papers were used to test for the presence of different agents. In 1941, "Detector Paper No. 1" was in use to check for L but a new paper (No. 5) had been developed [24].
 - Apart from detecting the presence of L the papers were designed to show, by the colour that they turned to, the likely effect on the skin (yellow generally meaning that the contamination was sufficient to redden the skin and orange indicating a danger of vesicles). The two papers were tested in 1941 to ensure that the paper reaction was an accurate indication of the danger to skin. Volunteers wore pieces of khaki serge on their arms with detector paper being inserted under one of the pieces.

L vapour was then directed onto both pieces and the skin reaction and the colour to which the detector paper turned were compared [24].

After World War II these protection studies continued but with some differences. All the studies considered liquid H and none of them were conducted while volunteers were wearing garments. With the advances in material science and technology the liquid H penetration test was used to evaluate candidate materials for future designs of protective clothing (during World War II existing protective garments were considered). Many hundreds of these tests were carried out until 1978 when work with H ended at Porton. Candidate NBC kit materials were also tested with liquid G agents and VX but these experiments were conducted using a drum mechanism and resected skin [25].

The entire range of protective fabrics tested in human studies after World War II to 1978 will not be listed here. However, the technique used remained much the same over the years [26]. All volunteers attending Porton continued to undergo the H sensitivity test and volunteers who showed a sensitivity to H were excluded from any H tests during their stay. Human tests of the degree to which H liquid penetrated fabrics were normally conducted on the forearm. Typically [26] a 3.5 cm square piece of protective clothing was held in close contact with the skin by an adhesive plaster. A 2.5 cm square hole had been cut in the middle of the plaster, thus exposing the protective material. A single drop of H was placed on the protective material and left for up to 6 hours. The assembly was covered to prevent the drop of H being accidentally transferred or touched so the volunteer could follow sedentary leisure pursuits without danger. After removing the assembly the arm was examined a day later.

There were some variations on this technique. Sometimes more than one drop of H was placed on the protective material; three [27] and five [26] were sometimes used. Although many such studies were conducted they did not take place without the approval of COSHE (after it was formed in 1963) which ruled on the number of drops, the precise drop size to be used (usually expressed as μg and typically varying from 125 - 2000 μg) and the length of time the assembly could be left on the arm [27, 28, 29, 30 as examples].

Another variation was the sleeve test [26] where a hole was cut into the sleeve of an otherwise complete NBC suit to expose part of the forearm. A piece of material being tested for future protective clothing was sewn into the hole. A volunteer would don the suit and a single drop of H would be placed onto the sewn piece of clothing. The suit would be worn over the next 6 hours during which time the volunteer was encouraged to walk outdoors or indoors.

20.2. Skin decontamination and treatment

20.2.1. Introduction

Human studies of the decontamination and treatment of skin exposed to chemical warfare agents fall into distinct categories, as outlined below.

- Decontamination of skin from liquid agents. Ointments, creams, cakes (having a similar constituency to lipstick) and powders dominated human studies. Occasionally other substances were tested as decontaminants and methods (dry swabbing or wet swabbing with various materials, for example) were also investigated. The nature of these studies was to apply a drop of liquid agent, usually H, L, HN-2 or HN-3, onto the skin of the arm. The drop was left for a short time, typically 2 minutes but sometimes longer, before the decontaminant was applied; this time is referred to in this section as the "delay". A volunteer taking part in such a study might have more than one drop of an agent, or more than one agent, applied to the skin so that different decontaminants could be applied and compared directly. Using more than one drop on each man meant that the analyses of the results were not confused by individual variation to the effects.

- Ointments as prophylactics. In describing the field trial in 1953 in which men were exposed to H vapour, it was noted that areas of the skin were protected by AG No. 5 Ointment. Many of the ointments, creams and cakes tested in human studies were assessed for their prophylactic value against H vapour. Usually an area of the skin was inuncted with ointment and, a certain time afterwards, the area was exposed to H vapour. The method of exposure was generally to place against the skin the mouth of a tube containing H vapour. Exposures normally lasted for 3 minutes. An untreated area of skin was often exposed so the prophylactic effect on the treated skin was more clearly distinguished.
- Irritancy of ointments and creams. Because ointments and creams might be used as a prophylactic against H vapour they were tested to see if they irritated the skin. Usually, they were applied daily to a shaven area of the face. Sometimes other sites were used.
- Treatment of mustard gas blisters. Two studies during World War II examined different ways of treating blisters produced by liquid H on skin. Drops of liquid H were applied to the arms but (in contrast to the decontamination studies) were left on the skin for longer to allow a blister to develop. Again, more than one blister might be induced on the arms of a man to allow treatments to be compared.
- Decontamination of hazardous liquids. In terms of method these studies were identical to other studies of decontaminants but the liquid used differed. For example, one study looked at ways of decontaminating the skin from liquids which were used as intermediates in the production of a lachrymator, DC.

During World War II thousands of volunteers took part in studies in the first three of these categories. The studies themselves can be separated into sustained efforts to find new and effective forms of ointments or creams and ad hoc studies which considered ointments as they became available (from industry, the Allied powers and from captured enemy equipment). Sustained studies were normally reported formally whereas ad hoc studies were not (often because the ointments or creams were found not to be as effective as existing ones).

The approach taken in this section is to use the sustained studies as examples of how this work was conducted and to give a list of ointments and creams used in ad hoc studies. For the latter, the name of the ointment or cream is given but some of the names are cryptic and no information has been found by the survey which describes why these names were chosen or what was contained in the ointments and creams. The human studies carried out after World War II were fewer in number and were dominated by the desire to find a single form of treatment that was effective against H and nerve agents. All of those studies are described.

20.2.2. Decontamination of the skin

During 1939 and 1940 much time and effort was devoted to evaluating ointments and creams in ad hoc studies [13, 14, 15, 16, 17]. It was usual to use Anti-Gas No. 1 (AG1) or AG2, existing ointments, for comparison. A summary of those studies is given in Table 20.1.

Cream/ointment	Agent	Site & drop	Men
Bleach paste, K6, K7, A, B, PK5, PK8, PK10, BDH, Chlor T, Ointments 27 & 28, benzoyl peroxide, antiflavoc, GCB, E1-E8, French ointment, phenyperit, ionolyth, CCI, No.1(Pink), No.2 (White), methylene blue treatment, Toronto solution, L9, L2, L10, L4, KLM cream, Octan, Z3, Z7, Z10, Z11, Z16, Emulsion X and Z [with AG2 or AG1 as control]	H	arm, 2 or 3 (mostly drops on same arm, sometimes 1 on each arm)	374
Yperatox and bleach paste, K6, K7, PK5, PK10 BDH, Chlor T, Ointments 27 & 28, benzoyl peroxide, E1-E8, phenyperit, ionolyth, antiflavog, GCB, CCI, No 1(Pink), No.2 (White), L2, L10, KLM cream, Octan, L4, Z3, Z7 [with AG2 or AG1 as control]	L	arm, 2 or 3	258
German anti-gas tablets - crushed and made into paste and applied to H v AG2. German bleach and Russian treatments v AG2	H	arm, 2	4
	H and L	arm, 3	3

Table 20.1. Ad Hoc studies 1939 and 1940

The remaining descriptions are of sustained studies which prompted formal reports. By 1939 several ointments had been developed to decontaminate the skin, notably AG No. 2 and AG No. 3. As new ointments were considered they were often compared to these established ones. The first new ointment developed was E9. Outlines of human studies are shown in Table 20.2.

Date	Tests	No. of men	Drops applied	Drops per man	Delay (mins)
1940	Comparison of E9 with AG No. 2 v HN-3 [31]	19	HN-3 ¹⁵ (2 mm)	2	2 or 5
1941	Comparison of Porton E9 with trade versions [32]	8	H (2 mm)	2 or 3	2
		8	L (2 mm)	2 or 3	2

Table 20.2. Studies with Ointment E9

In 1940 the General Staff sought an ointment which could be used in temperate and tropical conditions; AG No. 3 had been developed for this purpose but it was greasy and tended to seep badly from the tubes in which it was distributed [33]. A series of studies was conducted to develop a vanishing cream, rather than an ointment, which contained AV. Creams with different concentrations of AV and different oils were used. The studies are outlined in Table 20.3.

Date	Tests	No. of men	Drops applied	Drops per man	Delay (mins)
1941	Preliminary work with AV vanishing creams [33]	8	H or L (1.1mm)	2	2
		36	H (2 mm) or L (1.1mm or 2 mm)	2	2
1941	Additional work with V9 AV vanishing cream [34]	18	H or L (2 mm)	3	2
1941	Comparison of dry and wet V9 [34]	6	H or L (2 mm)	3	2
1941	Work with X151 AV vanishing cream [34]	4	H (2 mm)	5	2, 5 and 10
		4	L (2 mm)	4	2 and 5
1942	AV vanishing creams with peanut oil [35]	18	H (2 mm)	1	2
		18	L (1.5 mm)	1	2
		18	HN-2 ¹⁶ (2 mm)	1	2

Table 20.3. Studies with AV vanishing creams

¹⁵ In the report of this work, the agent is referred to as "T773".

¹⁶ Referred to in the report by its early wartime name, S.

By 1941 two new candidates to treat skin contamination by L had emerged: one was DTH (dimercaptopropyl alcohol or Dithiol, referred also as BAL), investigated by workers at Oxford [36] and the other, worked on in Canada, was hydrogen peroxide [36]. The two were compared in animal studies. A short series of human tests were then conducted with hydrogen peroxide. By 1943 DTH was supplied to the military in the form of a lotion for the treatment of eyes but was of limited value because it was too runny [37]. Human studies were conducted in 1942 and 1943 to develop an ointment form of DTH (or "US - BAL" as it was then referred to) which could be used to treat L contaminated skin. These studies are summarised in Table 20.4.

Date	Tests	No. of men	Drops applied	Drops per man	Delay (mins)
1941	Preliminary work with hydrogen peroxide [36]	6	L (2 mm)	2	2 or 5
1942-3	DTH vanishing cream ointments and solution ointments [37]	60	L (2 mm)	2	60
	Comparison of D19 and D20 DTH ointments [37]	6	L (2 mm)	3	60

Table 20.4. Studies with hydrogen peroxide and DTH ointments

Some studies investigated metallic based and acid based ointments. The first, in 1939, explored ointments containing zinc peroxide or magnesium peroxide because these had proved better than bleaching cream for decontaminating equipment [38]. In 1942 tannic acid, in the form of ointment, had proved better than the "standard decontamination by water" against HN-2 and was tested on volunteers [39].

In 1943 it was noted that when the skin was contaminated with a blister gas it was "in general, only during the next few minutes immediately following contamination that anything can be done to prevent a blister from developing" [40]. A large study tried to find a treatment which could be applied at any time after contamination to prevent vesication. The study initially explored 60 substances (including nembutal, chloroform, vinegar, ethyl alcohol and liquid paraffin) each one being tested by 2-6 volunteers. Those that did not prevent vesication were rejected. Various kaolin pastes and trichloroacetic acid (in dilutions from 10-50%) proved to be effective and these were studied further [40]. Silver nitrate and zinc chloride were also tested. These studies are summarised in Table 20.5.

Date	Tests	No. of men	Drops applied	Drops per man	Delay (mins)
1939	Ointments with zinc peroxide and magnesium peroxide [38]	8	H (1.1 mm)	2	2
		8	L (1.1 mm)	2	2
1942	Tannic acid ointment [39]	6	HN-2 (2 mm)	3	2
		9	HN-2 (2 mm)	2	2
		4	HN-2 (1 mm)	2	2
1943	Prevention of vesication: initial study of 60 substances [40]	210	H (1.1 mm)	2	240
	Kaolin pastes and acid [40] (see note)	79	H (1.1 mm)	2	5-720
		50	L (1.1 mm)	2	<240
		11	HN-2 (1.1 mm)	2	240
		13	HN-3 (1.1 mm)	2	240
	Silver nitrate [40]	34	H (1.1 mm)	2	240 or 120
Zinc Chloride [40]	34	H (1.1 mm)	2	240 or 420	

Note: H was also applied as liquid or vapour through clothing in this work. No details are given in the report but 166 men received H through clothing before treating the skin with kaolin paste or acid [40].

Table 20.5. Studies with Kaolin pastes and acids and metallic based ointments

In 1944 it was recognised that existing AG ointments were of limited value in tropical conditions [41] and a series of studies was conducted to explore new active ingredients to improve them [41, 42]. Included among the ingredients studies were AV (which is a chloroimide) and chloroimides used by the US. These studies are summarised in Table 20.6.

Date	Tests	No. of men	Drops applied	Drops per man	Delay (mins)
1944	New active ingredients: 34 compounds tested [41]	146	H (2 mm)	2	2
1944	Further work [42]: a. normal skin	20	H (2 mm)	2	2
		4	H (2 mm)	4	2
	b. sweaty skin (men exercised in hot room for 30 minutes beforehand)	8	H (2 mm)	2	2
		4	H (2 mm)	3	2
		10	H (2 mm)	4	2

Table 20.6. Studies of ointments for tropical conditions

A short study was carried out in September 1944 to investigate whether anti-flash creams prevented phosphorus burns [6]. Three men took part in the work and had 20 mg particles of phosphorus placed on each arm. Their left arm was untreated but their right arm had had anti-flash cream applied 30 minutes before the phosphorus contamination.

Work after World War II sought to find a suitable means for removing G agents from skin and studies were conducted with rabbits in 1949 and 1950 [43, 44]. The drill then in force for decontaminating the skin from liquid agents was based on "traditional" war gases but animal work showed that AG Ointment No. 6 was not effective as it converted sub-lethal doses of GB into lethal doses "presumably by hindering free evaporation" [43]. Dry swabbing was also found to be useless and possibly dangerous [43, 44].

This animal work prompted human studies in 1953 and 1954 to find a method of decontamination which was suitable for H and G agents so that a new drill could be devised [45]. Swabbing, flooding with water, blotting and picking off the liquid contaminant with gauze were tried in combination with ointments and powders (British and Dutch versions). Human studies were confined to H and L; GB work, using the same methods, was conducted with rats [45]. The study concluded that the decontamination drill should be modified to eliminate all swabbing and substituting flooding with water. Powders were found to be simple to use and effective against H, L and GB [45].

Further studies were carried out in 1955 with chloroimides (like AV or the US S330, CC-2 and XXCC-3) made up as "cakes" [46]. The consistency of most cakes was similar to lipstick and applied in a similar fashion to the skin. Some cakes had a consistency of soap. Human studies tested many cakes against H and Cake No. 2 was found to be the most satisfactory. It was then tested against liquid GB in animal studies [46].

The next series of studies in 1958 and 1959 tested cakes, powders and ointments and various materials (blotting paper, cotton waste, crepe tissue, asbestos and masslinn) [47]. Human tests were again confined to H. The same methods were tried against liquid V agents in work with rabbits [47]. The study concluded that the Dutch powder alone was as efficient as any other combination as a decontaminant for H, G and V.

The human studies of this series, from 1953-1959 are summarised in Table 20.7.

Date	Tests	No. of men	Drops applied	Drops per man	Delay (mins)
1953-4	Ointments, powders and methods for new drill [45]	71	H (2 mm)	2	2
		88	H (2 mm)	4	2
		10	H (2 mm)	6	2
		43	H (2 mm)	2	5
		12	H (2 mm)	4	5
		12	L (2 mm)	4	2
		6	Thickened H (2 mm)	2	2
		5	H/L 50/50 (2 mm)	2	2
	Tests in humid conditions [45] (see note) (see note)	38	H (2 mm)	2	2
		12	H (2 mm)	4	2
10		H (1.1 mm)	2	2	
1955	Study of cakes [46]	66	H (2 mm)	2	2
	Cake No. 2 in tropical conditions	24	H (2 mm)	2	2
1958-9	Materials alone [47]	80	H (2 mm)	2	2
	Ointments, powder, cake alone [47]	228	H (2 mm)	2	2
	Mixture of materials and ointments etc. [47]	95	H (2 mm)	2	2

Note: These 22 men underwent the procedure twice in different climatic conditions.

Table 20.7. Human studies 1953-1959

The next series of human studies with decontaminants concentrated on Fuller's Earth. In the early 1960s Fuller's Earth powder was assessed in chemical tests in the laboratory and found to be a good absorbent of liquid and able to remove V agents; Surrey Finest was deemed the most suitable powder for practical use [48]. Fuller's Earth was tested in human studies from 1960 to 1963 applied either as loose powder or from pads impregnated with powder [49].

- 24 men had four 200 µg drops of H applied to each arm and the delay before Fuller's Earth powder was applied varied from 1 minute to 3 minutes [49]. The drop diameter is not given but for comparison a 1.1 mm diameter drop of H contained 800 µg (in this work drops were placed on the skin with a microdropper so very small amounts could be applied). 12 other men were decontaminated using other solutions.
- 87 men contaminated in a similar fashion applied Fuller's Earth in pads to drops of H. This figure includes 12 men who applied Fuller's Earth powder as opposed to pads and 29 men who are listed in the experimental records in among the Fuller's Earth work but whose entries are annotated simply "H decontamination".

Occasional short human studies testing decontaminating methods were conducted after 1963.

- In May 1965 six men took part in a comparison of Norwegian and English decontaminating pads. Each of men had three 4 mg drops of H placed to each arm which was left for two minutes before the pads were applied [50].
- In August 1967 decontaminating pads were again tested in combination with washing with soap and water. Eight men took part, each having their arms washed with soap and water, after which two 50 µg drops of H were placed on their forearm. Two minutes afterwards the pads were used and 30 minutes later the arms were washed again with soap and water [51].

- The experimental records note that 16 men took part in "H decontamination" work in January and February 1974 [52] but there are no details of the nature of the study.

20.2.3. Prophylactics against H vapour

Many of the ointments tested as decontaminants for H were also assessed as prophylactics. Some of the creams and ointments investigated in ad hoc studies 1939 and 1940 (summarised in Table 20.1) were also tested as prophylactics against H vapour [13, 14, 15, 16, 17]. The ointments and creams considered include: K6, K7, benzoyl peroxide, E1, E4, PK8, PK10, PK11, PK12, No.1(Pink), No.2(White), phenyperit, antflavog, GCB, 5% iodine, octan, L2, L4, L10, Z3 and Z7. These were used to inunct a region of the arm and then H vapour was directed against the site for 2 minutes. In total 195 men took part.

The remainder of this section deals with the sustained studies of ointments and creams which prompted formal reports. Table 20.8 summarises the human studies conducted with H vapour against sites on the skin to which ointments or cakes had been applied. The ointments and creams in Table 20.8 are those which appeared in the sustained studies of skin decontamination (summarised in Tables 20.2 to Table 20.7).

Date	Tests	No. of men	Skin used	Number of sites per man	Exposure time (mins)
1941	Ointment E9 [32]	11	Arm	3	3
1941-2	AV vanishing creams [33, 34, 35]	7	Arm	3	3
		3	Arm	4 (each man had 4 sites exposed twice)	3
		4	Arm	3	4-10
		3	Wrist to elbow		60
1944	New active ingredients [42]	48	Arm	2	3-40
		8	Arm	1	20-90
		12	Neck	2	not specified
1955	Cake No. 2 [46]	6	Arm	10 (sites exposed on different occasions)	10-60

Table 20.8. Human studies with ointments as prophylactics

Additional to these studies 16 ointments were tested in 1944 as part of the work to find the one most suited for use in tropical conditions [53]. The way in which H vapour was used to test the prophylactic value of these ointments differed from the usual method. Here H vapour was applied for the time (or in the concentration) necessary to "cause breakdown of the ointment and the development of a lesion" [53]. Two types of tests were conducted as outlined below.

- The armpit was shaved and the ointment under test applied. H vapour was directed against the armpit through a tube (in the usual way) but the exposure continued until a lesion began to form. A total of about 350 exposures were conducted in this way. The report does not make clear how many volunteers were involved [53].
- Volunteers wore impregnated battledress, respirators and steel helmets. The exposed areas of the skin at the face, neck and hands were inuncted with the ointment under test. The men then spent 60 minutes in the climatic chamber in tropical temperature and humidity. Men were exposed to H vapour for 60 minutes. The concentration of H vapour used during these exposure varied to that "necessary to produce burns of casualty severity" [53]. About 290 exposures were conducted but the report does not specify how many men took part.

Table 20.9 summarises the studies in which the irritancy of ointments was assessed.

Date	Tests	No. of men	Skin used	Application
1941	Ointment E9 [32]	10	Chin/jaw	Repeated over one day. Men wore respirators in a hot room for 4 periods of 20 minutes at 2 hour intervals.
1941-2	AV vanishing creams [33, 34, 35]	4	Right side of face	Repeated over one day. Men wore facepieces in hot room for 3 periods, exercising during the first period
		10	Chin/jaw	Daily over 4 or 5 days to shaven area
		6	Thigh	Daily over 4 days
		6	Right side of scrotum	Daily for 2 days
1942-3	DTH vanishing creams [37]	6	forearm and upper arm	One application
1944	AV ointment toxicity(see note) [12]	12	Body	20g, 50g or 75g applied over "greater part of the skin surface of the body"
		9	Body	As above, but applied while men in hot room
1947-8	BAL Ointment [6]	24	Arm	Applied once
1955	Cake No. 2 [46]	19	Inner thigh	Daily over 4 days
		20	Scrotum	Daily over 4 days

Note: this work was part of the study to investigate the toxicity of AV impregnated clothing.

Table 20.9. Irritancy tests

20.2.4. Treatment of mustard gas blisters

In 1943 work was conducted to find a treatment for mustard gas blisters. It was noted that mustard burns took longer to heal than thermal burns of similar intensity and were believed to be prone to secondary infection. A treatment which prevented secondary infection and promoted skin growth had not been found by 1943 [54].

Volunteers who took part in the first study had liquid H applied to the forearm and upper arm so that burns were produced. Each subject had 8 burns: 4 small (covering 2 square cm) and 4 large burns (covering 6 square cm). Burns were treated 24 hours after contamination at which time the blister formed was more or less at its maximum size [54]. The roof of the blister and all epidermis was removed and one of the treatments under test applied. Each blister was dressed with another dressing being applied 3 days later. Fourteen days later the dressings were removed and the lesions treated according to their condition.

Twenty five treatments were tested with 60 volunteers. All the burns inspected just before the second dressing was applied on the third day were clean and healthy, irrespective of the treatment that had been tested. Powdered sulphathiazole was the best, with powdered sulphanilamide being almost as good but a little more painful when applied [54].

The report notes that "31 severe casualties from mustard gas burns have also been treated". Fourteen of these cases were caused by H vapour and 17 from clothes contaminated with liquid drops of H [54]. It is not clear where these 31 casualties came from or if Porton treated them or merely knew of the treatments used by the medics who did. Eleven of the seventeen who became casualties after their clothes were contaminated with liquid drops of H appear to have been Service volunteers who had taken part in an earlier field trial at Porton. This trial is covered in an earlier chapter but the medical report of the treatment of these 11 Service volunteers by Porton medics [55] suggests the lessons learned contributed to this study. Whether the remaining 20 casualties who were cited in this study were also Service volunteers who had sustained their burns during their time at Porton is unclear. From the treatments administered to the 31 casualties, acriflavine emulsion and powdered

sulphathiazole were found to be effective. Both were available to Medical Officers in the field [54].

The second study [56] later in 1943 considered the substances already available to Field Medical Officers which might prove useful for the treatment of mustard gas burns. Six substances were tested with 24 men each having 6 blisters induced by liquid H. The procedure used was the same as the previous study except that 12 men did not have the roof of their blisters removed.

Of the substances tested initially Gentian Violet Co Jelly proved to be the best. This was compared to sulphanilamide powders and acriflavine emulsion (two treatments noted in the report of the first study to be effective) and three other treatments. Twelve men took part each having 6 blisters induced by H liquid and in each case the blister roof was removed before the treatment was applied [56].

Comparisons were made between the healing of H burns and L burns. No details are given in the report of how many men took part but each man had three H burns and three L burns (each covering 2 square cm). Some of the blister roofs were removed, others left intact.

The conclusions drawn by the report were [56]:

- sulphanilamide powders and acriflavine emulsion again proved excellent in treating H burns and Gentian Violet Co Jelly was satisfactory;
- if the blister roof is left intact the burns heal quicker, give little pain and little or no sepsis;
- L burns heal quicker than H burns, are less prone to infection and cause less pain during healing.

20.2.5. Decontamination of hazardous liquids

A study was conducted during the period 1939-40 to consider the effect on the skin and methods of decontamination of two substances used in the manufacture of DC and posing "the most likely danger to personnel": phenyl dichloroarsine (abbreviated to "MA") and arsenic trichloride (AT) [57]. The two parts of the study are outlined below.

- The effects of the two substances were determined in tests with 18 volunteers. Each had one drop (of diameter of 0.75, 1 or 1.5 mm) of each substance placed on the arm. AT caused immediate reddening of the skin and MA induced vesication some hours after application.
- Eight treatments were tried including Ointment E9, AG No. 2, hydrogen peroxide and bleach cream. Three men took part in tests of these methods. Drops of diameter 1.1 mm and 2 mm of MA and AT were applied to the arm and treatments were tested immediately after and up to 5 minutes afterwards.

20.3. Other treatments

Five studies were conducted of treatments taken internally. It is not clear for which ailment these treatments were considered. They do not appear to have been investigated as part of the work into nerve agent poisoning and so are covered here.

In 1954 the effectiveness of cortisone acetate, given via IM injection or orally, in treating H burns was tested [58].

- Six volunteers had a 1 mm drop of H placed on each forearm which was allowed to dry and skin reaction was recorded every day over 9 days. Three men were given daily IM injections in the buttock of 50 mg of cortisone acetate.

- Six other volunteers underwent the same procedure but 3 were given cortisone acetate orally, 100 mg per day, instead of by IM injection.

The effect of Moryl (referred to as "carbamylocholine chloride") [58] on blood pressure and pulse was tested in October - December 1954. Twenty volunteers received 0.5 mg by IM injection in the buttock. A further 30 received one oral dose in 100 ml of water of 4 mg, 6 mg, 8 mg or 10 mg.

In November 1954 the effect of probanthine on pupil size, pulse and blood pressure, when given orally was tested [58]. Six volunteers took a dose of 30 mg and 6 a dose of 60 mg.

In December 1954 ten volunteers took part in a study of the effect of tolazoline on pulse and blood pressure, each receiving 10 mg by IM injection [58].

In May 1976 four volunteers were given 60 mg of ephedrine hydrochloride [59] and 3 other volunteers served as controls. The heart rate and blood pressure of each man was monitored over 5 hours and taken again 24 hours after dosing. It is not clear why ephedrine hydrochloride was considered; no mention of it has been found in other documents. It may (or may not) be relevant that in 1949 when atropine was in short supply the BC considered alternatives as treatments for nerve agent poisoning. One of the alternatives mentioned by the BC was "ephedrine" which was rejected because its effect was deemed too short [60].

20.4. Eye treatments

In 1943 DTH lotions (containing BAL) were being supplied to the Services for the treatment of eyes contaminated with arsenicals [37]. The work in 1943 in producing a DTH (or BAL) ointment rather than a lotion has been outlined in Section 20.2. Three ointments developed under that work were referred to as D12, D19 and D20 (the "D" meaning decontaminant). These ointments were made up of a base and a concentration of BAL.

The effectiveness of these three ointments and one other (D7) in treating eyes contaminated with L was compared to the effectiveness of the existing lotions in rabbits [37, 61] in 1943. Whether the three ointments caused any irritation was tested in human studies, an outline of which is given below [37].

- Thirty one men took part: each had 50 mg of the existing DTH lotion, or D12 or D19 applied to one eye. The substance was applied either directly by a member of Porton staff or the amount was placed on the man's finger, who then rubbed the substance along the lid of the eye.
- Five of these thirty one men had the base (i.e. without the BAL component) of one of the ointments (D12, D19 or D20) applied to the other eye.
- The application of the ointments and the lotion invariably caused immediate discomfort, which continued for up to 30 minutes. One man was reduced to sobbing and the pain was abolished by the application of cocaine.

The study concluded that D19 and D20 were the best two ointments. As the base used for D19 was not readily available D20 was recommended. The effectiveness of D20 against H and L contamination of the eye was studied further in rabbits [62]. D20 containing 5% BAL and 10% were tried, the latter being found to be best.

The next studies relating to the treatment of eyes were concerned with the effects of G agents. The first part of the work exploring the effect of GB vapour on the eyes reported in 1951 [63]. Atropine, lachesine and phenergan were applied before or at various times after men had been exposed to GB at an exposure level in the range 6.5 - 36.7 mg.min/m³ (t generally around 2 minutes). Men exposed at levels above 14 mg.min/m³ wore oro-nasal respirators. Atropine was applied in either a 0.25% or 1% solution to the eyes of 12 men.

Lachesine as a 1%, 5% or 10% solution was applied to the eyes of 32 men and phenergan was tested in 7 men. The results of the work were as follows [63]:

- one drop of atropine as 1% solution gave great relief from the pain and general symptoms experienced by the men but did not prevent miosis;
- one drop of 10% lachesine was as effective as a drop of 1% atropine.

The next study, in 1952, concentrated on atropine [64]. 1% atropine drops had been recommended to the Services for the treatment of eye effects but no systematic exploration had been mounted into the best method of administering atropine [64]. The study involved 48 volunteers who were exposed to either GA or GB at about 10 mg.min/m³ (t = 2 minutes). Atropine ointment and drops were tested in strengths of 0.1%, 0.25%, 0.5% and 1%. The details of the work are summarised below.

- Twenty men were exposed to GB at 9.8 - 10.7 mg.min/m³. Twelve men had one eye treated with drops, the other with ointment. Four men had drops to both eyes and 4 had ointment to both eyes. In each case the treatment was given 2 hours after exposure to GB.
- The work was repeated with another 20 men but this time the exposure was to GA at 9.6 – 9.9 mg.min/m³.
- Eight other men were exposed to GA of around 10 mg.min/m³ and received treatment either 2 hours or 5 hours afterwards.

The work recommended the 0.25% atropine preparations and noted that against GA a repeat dose may be necessary.

The final study on eye treatments was carried out in 1960 with P₂S as it was thought to be more advantageous than atropine drops which left the pupils dilated [65]. Initially the effect of P₂S on the eyes was tested in 57 men. The left eye was irrigated for 2 minutes in an eyebath containing a 15% solution of P₂S. No changes were observed to the eye immediately afterwards or one hour later. The men complained only of a slight irritation, similar to that caused by salt water. Ten men were then exposed to GB at a level of 7.5 P₂S (t = 5 minutes), and the left eyes irrigated with a 15% solution of P₂S for 2 minutes, once 10 minutes after the exposure and again 10 minutes later. The eyebath was found to have no effect on miosis.

A proposal was made to COSHE in November 1969 to conduct further human studies with P₂S eyedrops [66]. However, COSHE did not approve the proposal noting that there was no great urgency for the study. No further mention of this proposal or P₂S eyedrop studies has been found in subsequent records.

20.5. Decontamination Methods

During World War II many methods of decontaminating clothing and equipment were considered. The way in which these studies were conducted is typified by the impregnated sock study (related in the section dealing with impregnated clothing) which showed that it was important to decontaminate boots even after they had been left in the open for several days. Work was conducted a month or so after the sock study in 1939 to test procedures for the decontamination of leather boots [67].

- Pieces of leather were taken from boot uppers and soles and contaminated with drops of H or HS. They were then decontaminated (using a variety of procedures) and separated into their three layers. The layers were worn in close contact with the skin of the arm by volunteers for a period of 1, 2, 4 or 18 hours.

This method of decontaminating pieces of clothing and then applying them to the arm was also applied to equipment. One example is a study of the decontamination of leather articles

[67], carried out in 1939. Various leather articles in Service use were considered: tool bag, waist belt, pistol case, the bayonet frog, ammunition pouch, greatcoat strap and the valise case. Six pieces from each article were decontaminated after having had drops of H applied to them and placed on the skin of the forearm. In contrast to the boot study, the pieces were kept on the arm for only 2 hours.

The decontamination of foodstuffs contaminated with H vapour, rather than H liquid, was investigated in a similar fashion. Typically food was contaminated with H vapour for an hour; the food was then decontaminated and pieces of it were placed on the skin of the arm and kept there for a period of time to see if any irritation was induced [18]. Examples of the food considered are listed below.

- Lean and fatty meat, beans and spaghetti decontaminated by boiling, placed on the skin for 1 hour in studies in 1939, 1940 and 1941 [13, 14, 15].
- Sugar, flour, butter, potato and margarine, decontaminated by airing and placed on the skin for 4 hours (1940 and 1941) [16, 18].
- Bacon (which was contaminated by being left for one week against the woodwork of railway truck previously contaminated with H) and then placed on the skin for 15 minutes (1942) [20]
- Tin of meat roll, decontaminated (by boiling or steaming), sliced and placed on the skin of the arm for 4 hours (1942) [21]
- Potatoes, grain, rice, green vegetables, flour, cheese, lard, sugar, tea and fruit contaminated with H vapour, either lightly (by exposure to a concentration of 10 g/m^3) or heavily (a concentration of 300 g/m^3). The food was decontaminated by various methods (hosing, washing, separation and airing, trimming) and then placed in contact with forearm skin for either 2 or 4 hours (1943) [22].

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