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Behavioral Efficacy of Diazepam Against Nerve Agent Exposure in Rhesus Monkeys[1,2]

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CASTRO, C. A., T. LARSEN, A. V. FINGER, R. P. SOLANA AND S. B. McMASTER. *Behavioral efficacy of diazepam against nerve agent exposure in rhesus monkeys.* PHARMACOL BIOCHEM BEHAV **41**(1) 159–164, 1992.—The possibility that nerve agents will be used on the battlefield is real. The traditional therapy against nerve agent exposure consists of pyridostigmine pretreatment and atropine-pralidoxime chloride therapy administered after nerve agent exposure. This therapy regimen is extremely effective in preventing mortality in laboratory animals exposed to multilethal concentrations of nerve agent, yet these animals often display convulsions, brain damage, and behavioral incapacitation. We report here that the addition of diazepam to the traditional therapy for nerve agent (soman) exposure not only decreases the incidence of convulsions, but also attenuates the cognitive impairments of rhesus monkeys trained on a Serial Probe Recognition (SPR) task. Monkeys which received diazepam treatment required only 6 days before their performance on the SPR task returned to presoman exposure levels, compared to nondiazepam-treated monkeys which required 15 days. Moreover, only 1 out of the 5 monkeys which received diazepam treatment suffered tonic-clonic convulsions; in contrast all 5 monkeys which did not receive diazepam treatment experienced severe convulsive episodes. These results suggest that diazepam would be an excellent adjunct to traditional nerve agent therapy to facilitate behavioral recovery from nerve agent intoxication that might be encountered by US military personnel on the battlefield or accidental organophosphate poisoning encountered in industrial or agricultural accidents.

Serial probe recognition (SPR) Diazepam Nerve agents Soman Convulsions Rhesus monkeys Cognition Organophosphate

SOMAN is an extremely toxic organophosphorus chemical warfare nerve agent capable of producing death in humans and experimental animals within minutes of exposure (16). Soman primarily produces its toxic effects by rapidly and irreversibly inhibiting acetylcholinesterase activity which leads to excessive acetylcholine accumulation at synaptic sites. This rapid increase in acetylcholine produces hyperstimulation of the cholinergic receptors and is related to the clinical signs observed in organophosphorus intoxication, such as profuse salivation, involuntary urination and defecation, lacrimation, muscle fasciculation, severe ataxia, whole-body tremors and convulsions (1,10). Death usually results from respiratory failure (4,12). The standard treatment for organophosphate poisoning involves a combination of carbamate pretreatment and anticholinergic-oxime therapy. The carbamate pyridostigmine is given as a pretreatment prior to organophosphate exposure, since it reversibly binds to acetylcholinesterase, thus, protecting it from being permanently inactivated by the nerve agent. The anticholinergic atropine, which ameliorates the muscarinic action of excessive acetylcholine, and the oxime pralidoxime chloride (2-PAM), which reactivates the inhibited acetylcholinesterase, are given as treatment after organophosphate exposure.

The pretreatment of nonhuman primates with pyridostigmine followed by atropine and 2-PAM therapy results in a significant improvement in the ability of these primates to survive exposure of multilethal concentrations of soman (5, 8, 11, 17, 22). Currently, this treatment strategy has been adopted by the U.S. Army for use by the individual soldier in the form of self-aid and/or buddy-aid in the event of nerve agent attack on the battlefield. Unfortunately, this therapy has not proven effective in protecting laboratory animals against the convulsions, brain damage, and behavioral incapacitation that also result from organophosphate poisoning at higher exposures (3, 15, 23). For example, it was recently demonstrated in nonhuman primates given the standard nerve agent regimen that 3–5 times the estimated median lethal dose (MLD) of soman (a) produced severe tonic-clonic convulsions, (b) impaired performance on the Primate Equilibrium Platform (PEP) apparatus, a task designed to model

[1]The opinions and assertions contained in this report are the private views of the authors and are not to be construed as official or as reflecting the views of the Army or the Department of Defense.

[2]In conducting the research described in this report, the investigators adhered to the Animal Welfare Act and the *Guide for the Care and Use of Laboratory Animals*, NIH Publication No. 86-23.

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the performance of aircraft crew, and (c) produced neuronal degenerative and necrotic lesions in the entorhinal and frontal cortices, caudate nucleus, and hippocampus (3, 13–15, 17, 23). However, with the addition of the anticonvulsant diazepam to the traditional nerve agent treatment regimen, the duration and incidence of the convulsions were significantly decreased, the performance decrements that occurred at later time points on the PEP apparatus were prevented, and the brain damage was lessened or completely prevented (13–15, 17, 23). These findings suggest that diazepam might be an effective treatment for not only preventing soman-induced convulsions and subsequent brain damage, but also reducing the ensuing behavioral incapacitation.

The purpose of this study was to determine whether the addition of diazepam to the standard nerve agent regimen could reduce these soman-induced behavioral impairments in a nonhuman primate using a task which measures cognitive function. The behavioral task selected for this study was the Serial Probe Recognition (SPR) task (18). This task was chosen because (a) it is a multiple item memory test which measures not only vigilance and sensory integration, but also short-term memory capacity and decision making ability (19,25), (b) it has been used extensively to understand human cognitive processing [e.g., (24)], and (c) it is a test known to be sensitive to CNS damage in both humans and nonhuman primates; for instance, rhesus monkeys with damage to the limbic system and humans suffering from amnesia as a result of either Parkinson's or Alzheimer's disease show impaired performance on a SPR task (7,20). Thus, if diazepam is able to protect against the behavioral incapacitation that results from soman exposure in nonhuman primates, whether it is a cognitive or physical impairment, it is likely that humans would also be protected.

METHOD

Experimental Animals

Ten naive, domestically born, rhesus monkeys (*Macaca mulatta*) of Indian origin, weighing between 2.3 and 2.7 kg at the beginning of the experiment, served as subjects. They were purchased from Laboratory Animal Breeders and Services (LABS), Yemassee, SC and maintained under an AAALAC accredited Animal Care and Use Program by the Veterinary Medicine Division, US Army Medical Research Institute of Chemical Defense. These monkeys were individually housed in stainless steel, squeeze-back cages (61 cm W × 71 cm D × 86 cm H). They were provided with commercial certified primate rations (Purina Mills, Inc., St. Louis, MO) twice daily and tap water ad lib. The monkeys' diet was supplemented with fresh fruit (oranges, grapes, bananas, or apples, depending on availability) three times each week. Animal rooms were maintained at 20–22 degrees Celsius, relative humidity of 50% (±10%) using at least 10 complete air changes per hour of 100% conditioned fresh air. The animals were on a 12-hour light/dark cycle with no twilight, lights on at 0600. The animals were returned to the institute primate colony at the completion of the study.

Serial Probe Recognition (SPR) Task

Apparatus. The subjects were tested unrestrained in one of eight large primate test chambers (61 cm W × 61 cm H × 61 cm L) constructed of Plexiglas® and stainless steel. The walls of the test chambers were constructed of black Plexiglas® and the top of clear Plexiglas®, with the bottom made of stainless steel grid poles (1.5-cm diameter grid bars spaced 2.5 cm apart). The test chambers were housed in a sound- and light-attenuated room equipped with a ventilation fan and two dehumidifiers. Each test chamber was also equipped with its own ventilation fan. The room lights were adjusted to dimly illuminate the test chambers. An Elographics (Oakridge, TN) serial touch screen (Model MBL E-264-13), 26.5 cm W × 21.5 cm L, was attached to the front wall of each of the test chambers, adjacent to the entrance. A Zenith high-resolution analog RGB color video monitor (Model MDL 1390) was positioned in the front wall of each of the experimental cages so that it was encased by the touch screen. Reinforcement (a 300 mg banana flavored pellet, Bioserve™ Inc., Frenchtown, NJ) was delivered by a pellet dispenser (BRS/LVE Model QNB-4001) attached to the outside of the chamber and out of reach of the monkey. The food receptacle was positioned in the front of the test chambers, centered directly under the touch screen and 2 cm from the chamber floor. A speaker was located directly above the touch screen. A Zenith microcomputer (Model ZXW-248-68) interfaced to the touch screen controlled all the experimental events and collected all the data. The stimuli consisted of 210 various objects, such as animals, transportation vehicles, toy objects, food items, and other miscellaneous objects. The size of the objects ranged from 2.5 to 7 cm in length and consisted of many different colors. Two stimulus objects could be presented at the same time, one object above the other. The center for the top object was displayed 11.5 cm from the top of the touch screen and 7.5 cm from the left edge of the touch screen. The center for the bottom object displayed 7.5 cm directly below the center of the top object. A white illuminated box (5 × 5 cm) was also displayed 24 cm from the top of the touch screen and 2 cm from the right edge of the touch screen. Throughout training and testing, all monkeys were monitored through the top of the primate test chambers using Panasonic video recorders (Model AG 170) and monitor/players (Model AG 500R).

Training procedures. Training was conducted in four stages. During the *preliminary training* stage, all monkeys were taught to enter and exit a stainless steel transport cage to permit transfer between their home cage and the test apparatus. As soon as transfer training was completed, the monkeys were trained to press the touch screen with their hands using standard shaping procedures. The *same-different discrimination training* stage began as soon as the monkey consistently approached and pressed the touch screen. A trial began with the presentation of two objects and the white illuminated box. On *Same* trials, the stimuli presented were identical. On *Different* trials, the stimuli presented were two nonmatching objects. The monkeys' task was to classify the objects as either the same or different. If the objects were the same (or matched), the monkey must touch the screen area where the bottom object was being displayed to receive a reinforcement. If the objects were different (or nonmatching), the monkey must touch the white illuminated box to receive a reinforcement. Same and Different trials were presented in a pseudorandom sequence and occurred with equal frequency at the beginning and end of each session. The *delayed same-different training* stage began when the monkey responded correctly on 80% of the probe trials on the same-different conditional discrimination problem. In this stage, a stimulus object (list item) was displayed in the top left position for 3 s, the list item was removed from view, and a stimulus object (probe item) was displayed in the bottom left position and the white box was illuminated. Reinforcement contingencies for the same/different responses were the same as those used in earlier training sessions. When the monkey responded correctly on 80% of the probe trials during the same-different discrimination training stage, performance was transferred to the multiple-item *serial probe recognition (SPR) training* stage by gradually introducing more than one list item (one at a time) in the top left position of the screen. This was accomplished by increasing the number of list items by one until six-item lists were presented. Monkeys

were advanced to the next higher list number after reaching an 80% correct performance criterion for 3 consecutive days.

Throughout testing and acquisition, items were displayed for 3 s with a 1 s delay between successive items. The probe item was displayed 1 s after the last list item and remained on until a response was made or 10 s had elapsed. Correct responses were followed immediately by a short tone (4000 Hz, 0.25-s duration), a reinforcer, and a 1.5 s intertrial interval. Incorrect responses were followed by a short tone (800 Hz, 0.25-s duration), the omission of the reinforcer, and a 1.5 s intertrial interval. If a monkey failed to make a response within 10 s of stimuli presentation, the trial was terminated by a short tone (800 Hz, 0.25-s duration), the omission of the reinforcer, and a 5 s intertrial interval. Probe items matched target items at each serial position with equal frequency on Same trials. On Different trials, probes were stimulus objects that were not contained in any list for that session. Each monkey received two 50 trial sessions per day, 5 days a week. Two weeks prior to soman challenge, the number of training days was increased to 7 days. This was done to acclimate the monkeys to daily trial sessions since following soman challenge, all monkeys were tested daily.

Drugs and Drug Administrations

All primates were pretreated with pyridostigmine, administered via a subcutaneously implanted osmotic minipump 3 days before soman challenge (Alza Corp., Palo Alto, CA, Model 2ML2 or 2ML1). The pumps were filled with a pyridostigmine concentration that would allow for delivery of 0.70 mg/kg/24 h. This dose has been previously shown to produce approximately 40% chronic inhibition of serum ChE activity (2). Animals were anesthetized with Telazol® [(3.0 mg/kg, IM) (A. H. Robins, Richmond, VA)] for the surgical implantation of the pumps. Following surgical preparation of the site, a 2-cm incision was made in the skin between the scapulae. A 5-cm long subcutaneous pocket was created by blunt dissection, the pump inserted into the pocket, and the incision closed with interrupted sutures. Approximately 1 h after soman exposure, the pump was removed from the locally anesthetized area of the unconscious monkey and the opening sutured closed.

Soman (0-1,2,2-trimethylpropylmethylphosphonofluoridate), 99.7% pure, was obtained from the Chemical Transfer Facility (CTF) of the U.S. Army Chemical Research, Development and Engineering Center (CRDEC), Edgewood, MD. To ensure the lethality of the soman challenge, a standard mouse potency check was conducted prior to primate exposure (23). Dilutions of soman for the mouse potency checks and the primate challenges were made in saline.

Atropine in citrate buffer, 2-PAM (pralidoxime chloride) in sterile water, pyridostigmine in sterile water and diazepam (5.0 mg/ml) diluted in vehicle consisting of 40% propylene glycol, 10% ethanol and 50% water were supplied by the Division of Experimental Therapeutics, Walter Reed Army Institute of Research, Washington, DC.

Cholinesterase and Acetylcholinesterase Assays

Plasma cholinesterase (ChE) and red blood cell acetylcholinesterase (RBC AChE) levels were determined approximately 1 h prior to minipump implantation (baseline), 1 h prior to soman exposure, and 1 h after soman exposure. Animals were restrained in primate chairs (Primate Products, Redwood City, CA) and a 1-cc blood sample was drawn from the saphaneous vein using a 23-gauge, 1-inch needle affixed to a 3-cc syringe. Plasma ChE and RBC AChE activity levels were determined using a modification of the automated continuous flow method (9).

Experimental Design

Upon completion of SPR training, the monkeys were divided into two equal groups (n = 5 per group). All monkeys were injected with a 5-median lethal dose (MLD) of soman (38 μg/kg) into the right gastrocnemius muscle while they were restrained in a primate chair. One min after soman exposure, atropine (0.2 mg/kg, IM) and 2-PAM (25.7 mg/kg, IM) were injected into separate muscle masses of the upper left leg of all animals. The two groups differed only in the amount of diazepam given. One group received 214 μg/kg of diazepam and the second group did not receive diazepam treatment. Diazepam was injected into a muscle mass of the right upper leg of monkeys assigned to the diazepam-treated group. The order of treatment was atropine, 2-PAM, and diazepam. These doses of atropine, 2-PAM, and diazepam have been shown to prevent lethality in rhesus monkeys challenged with 5 MLD of soman (23). Additional atropine injections (0.2 mg/kg, IM) were administered if signs of soman poisoning, such as severe salivation and congestion of lungs and trachea persisted. All animals but one received one additional atropine (0.2 mg/kg, IM) treatment. Additional diazepam (214 μg/kg, IM) was administered to one monkey assigned to the diazepam-treated condition. Under no conditions did the monkeys assigned to the nondiazepam group receive diazepam. Clinical signs of soman poisoning such as loss of consciousness, fasciculations, tremors, sweating, salivation, and convulsions were continuously monitored and recorded for at least 2 h after soman challenge. Performance on the SPR task was then assessed on the day of soman challenge and every day thereafter for at least 21 days.

RESULTS

Cholinesterase and Acetylcholinesterase Inhibition

The percent inhibition (±S.E.M.) of plasma ChE and RBC AChE 1 h prior to soman exposure was 42.1 ± 2.2 and 46.2 ± 1.3, respectively for the diazepam-treated group; and 38.0 ± 2.5 and 45.7 ± 2.7, respectively, for the nondiazepam-treated group. One hour after soman exposure, the percent inhibition of plasma ChE and RBC AChE was 95.7 ± 0.8 and 91.9 ± 2.1, respectively for the diazepam-treated group; and 97.3 ± 0.5 and 96.1 ± 1.1, respectively, for the nondiazepam-treated group.

Clinical Signs

Table 1 shows the number of convulsions, the length of the convulsive episodes, and recovery of SPR performance for the diazepam- and nondiazepam-treated groups. Convulsions were defined as tonic-clonic contractions of muscle groups or limbs, a convulsive event may have been intermittent or sustained and may have been brief (s) or lasted several minutes per event. The length of the convulsive episode was the time (s) from the onset of the first convulsion to the offset of the last convulsion. No convulsions were observed beyond one hour following soman exposure. Recovery of SPR performance was defined as the number of test days each monkey required before its performance reached at least 90% of its presoman exposure levels for three consecutive days. Diazepam significantly reduced the incidence of soman-induced convulsions (Fisher exact probability test, $p<0.05$). Whereas all five of the nondiazepam-treated monkeys suffered severe tonic-clonic convulsions, only one of the five diazepam-treated monkeys did so. Moreover, the length of the convulsive episodes was significantly correlated with the length of time for behavioral recovery on the SPR task, indicat-

TABLE 1

INCIDENCE OF CONVULSIONS, LENGTH OF CONVULSIVE EPISODE AND RECOVERY OF SPR PERFORMANCE OF DIAZEPAM- AND NONDIAZEPAM-TREATED RHESUS MONKEYS

	Mean ± S.E.M. (n)	Recovery of SPR Performance Corr.	*p*-Value	r^2
Nondiazepam				
No. of Convulsions	7.6 ± 3.0 (5)	.118	0.345	.125
Length of Convulsive Episode (s)	538.0 ± 115.5 (5)	.997	0.005	.994
Recovery of SPR Performance (day)	21.0 ± 7.3 (5)*	—	—	—
Diazepam				
No. of Convulsions	3 (1)	.272	0.717	.074
Length of convulsive Episode (s)	210 (1)	.272	0.717	.074
Recovery of SPR Performance (day)	6.2 ± 0.7 (5)*	—	—	—

*The diazepam-treated group required fewer test days on the SPR task before their performance returned to presoman challenge levels compared to the nondiazepam-treated group, $F(1,9) = 12.13$, $p < 0.007$.

ing that the more severe convulsions resulted in longer behavioral recovery.

The clinical signs of soman intoxication such as salivation, sweating, muscle fasiculations, and tremors were not prevented by the addition of diazepam, as all monkeys showed these signs of hypercholinergic stimulation (data not shown). In addition, nine of the ten monkeys lost consciousness within 2 min following soman challenge and remained unconscious for a period of 1–2 h. The exception was one monkey in the diazepam-treated condition which never lost consciousness. Parenthetically, it was this monkey which began responding on at least 90% of the probe trials within 4 h of soman challenge (see Fig. 1a and b). Furthermore, this monkey required only 5 days of testing before its performance returned to 90% of its presoman exposure levels, the quickest recovery of all animals tested.

Serial Probe Recognition (SPR) Task

The addition of diazepam to the nerve agent pretreatment and treatment regimen resulted in an attenuation of the behavioral impairments produced by soman exposure (Fig. 1a). The main effects of group and days, and the group × days interaction were reliable; all F values >6.01 and all *p* values <0.004. Subsequent analysis revealed that the diazepam-treated group was performing at 90% of their presoman exposure levels by day 6 (Newman-Keuls, $p < 0.01$). In contrast, the nondiazepam-treated group did not perform at their presoman exposure levels until day 15 (Newman-Keuls, $p < 0.01$), although all of them were responding on at least 90% of the probe trials.

At no time was there a difference between the diazepam- and nondiazepam-treated monkeys in their latency to respond on the probe trials (Fig. 1b). All F values were <0.94 and all *p* values were >0.54.

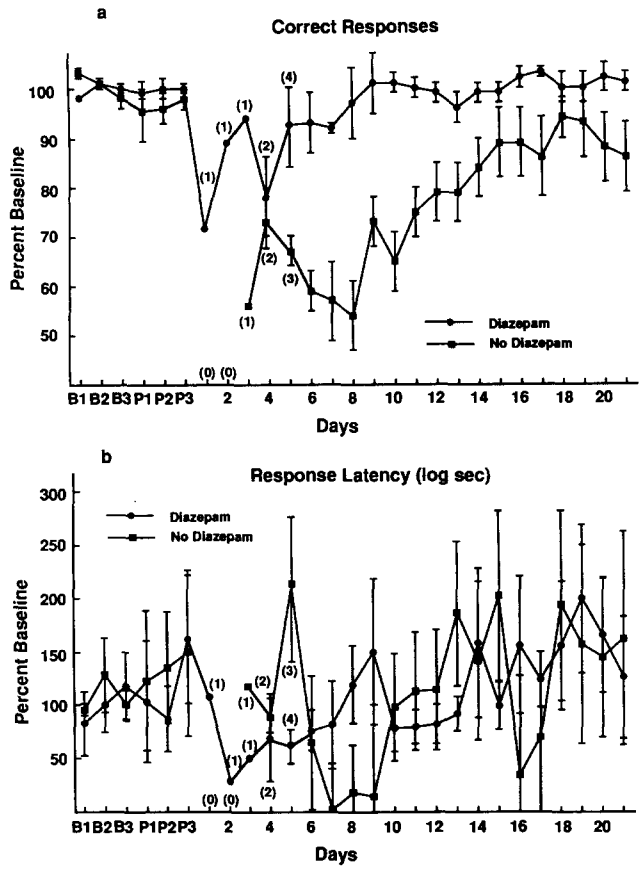

FIG. 1. The percent baseline of the number of correct responses (a) and the response latency (b) of the diazepam- and nondiazepam-treated groups trained on the SPR task before and after soman challenge relative to the mean of their 3-day baseline period. B1–B3 represent the 3 days of baseline performance; P1–P3 represent the 3 days of performance during pyridostigmine pretreatment, with P1 being 4 h after pyridostigmine treatment began; and days 1–21 represent performance following soman challenge, with day 1 being the day of soman challenge. All data points represent the performance of 5 monkeys except where indicated in parenthesis. Only the data for those monkeys which responded on at least 90% of the probe trials is plotted.

DISCUSSION

The major finding of this experiment is that the addition of diazepam to the standard nerve agent treatment regimen significantly attenuated the behavioral impairments produced by nerve agent exposure. The performance of the diazepam-treated monkeys on the SPR task recovered significantly quicker than the nondiazepam-treated monkeys. Since the SPR task is a test designed to assess cognitive function (see the Introduction), it appears that diazepam reduced nerve-agent induced behavioral incapacitation by attenuating or preventing cognitive impairments produced by nerve agent exposure.

However, one must consider the possibility that the behavioral impairment observed in the nondiazepam-treated monkeys on the SPR task does not in fact reflect a cognitive impairment, but instead a sensory, motor, or motivational deficit. Certainly, the observation that several of the nondiazepam-treated monkeys, as well as several of the diazepam-treated animals, did not respond on the probe trials during the first five days after soman challenge could be attributed to one or all of these nonassociative deficits. There is nothing from the present data to rule out this possibility. However, several aspects of the data argue against attributing the behavioral impairment of the nondiazepam-treated monkeys to these nonassociative deficits after this time. First, all of the nondiazepam-treated animals responded on

at least 90% of the probe trials on day 6 after soman challenge (see Fig. 1a). Second, at no time was there a difference in the response latency between the diazepam- and the nondiazepam-treated monkeys (see Fig. 1b). And third, when the nondiazepam-treated monkeys did make a correct response they readily consumed the food reinforcement. Thus the nondiazepam-treated monkeys appeared to possess the necessary motor skills to respond on the probe trials, appeared to possess the necessary sensory skills to see the stimuli and discriminate when a probe trial occurred, and appeared to be motivated to obtain the food reinforcement.

The difference between the diazepam- and nondiazepam-treated animals, therefore, would appear to lie in the integrity of the cognitive processes that enable the monkeys to perform accurately on the short-term memory (SPR) task. Given that soman exposure is known to produce neuronal degenerative and necrotic lesions in the neural systems that are important for short-term memory processing (i.e., the entorhinal cortex, caudate nucleus, and hippocampus) of pretreated and treated rhesus monkeys, and given that the addition of diazepam to the treatment regimen is known to decrease or eliminate this brain pathology, one hypothesis is that diazepam attenuated the behavioral impairment on the SPR task by preventing or lessening this brain damage. The results of the present study are consistent with this hypothesis.

One can only speculate about how the monkeys recovered their ability to perform on the SPR task after soman challenge. Assuming that the deficit does reflect an effect of soman exposure on the entorhinal, caudate, and hippocampal systems, one possibility is that functions normally mediated by these brain structures are taken over by some other neural system(s) (6). Another explanation is that one or all of these systems eventually become functional to permit SPR performance (6). By either account, the nondiazepam-treated monkeys are impaired relative to the diazepam-treated monkeys because more of their neural system(s) is lost or damaged due to soman exposure. Consequently, it takes longer for their system to recover the threshold number of neural elements (such as neurons, synaptic connections, dendritic arborization, etc.) needed to mediate SPR performance. An interesting implication of both accounts is that upon the return of performance to presoman exposure levels, the nondiazepam-treated animals would perform with less capacity than normal or diazepam-treated monkeys. To a much lesser extent, the diazepam-treated monkeys also would be performing with less capacity than normal monkeys. This might place both groups of monkeys at a disadvantage if they were tested under suboptimal conditions or tested on a novel behavioral task.

In conclusion, our results indicate that the addition of diazepam to the current therapy for nerve agent intoxication reduced the incidence of convulsions and cognitive impairments produced by soman exposure, although other important clinical signs were not reduced. We are continuing to evaluate other pretreatment and treatment combinations so that an even more efficacious therapy against nerve agent intoxication might be obtained. It is hoped that by obtaining a therapy regimen which prevents both physical and behavioral incapacitation, eventually nerve agents will no longer be effective as a chemical warfare agent.

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