Meeting of the Research Advisory Committee on Gulf War Veterans' Illnesses.
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Relevance of research to Gulf War Veterans and Veterans and Active Military of OEF and OIF operations.

1. Intranasal (IN) Delivery of Molecules Directly to the Central Nervous System (CNS).

Intranasal delivery is non-invasive and permits compounds that do not readily cross the blood-brain barrier (BBB) to bypass the BBB and be rapidly and directly delivered to the CNS along the olfactory and trigeminal nerves. Reduces systemic exposure and side effects.

Double-edged sword:
• Neurotoxins: For example, 1-methyl-4-1,2,3,6-tetrahydropyridine (MPTP). A single IN dose produces behavioral and histological indicators of Parkinson's Disease (PD). Repeated dosing over 21 days in rodents mimics the cognitive and motor impairments of PD. Insecticides, pesticides, and insect repellants??

• Neuroprotective agents: Intranasal insulin reverses many of the memory deficits of Alzheimer's Disease (AD) in humans—type 3 diabetes. In mice, IN deferoxamine (DFO, a high-affinity iron chelator) improves cognitive function and slows the loss of spatial memory in a transgenic model of AD. In rats, IN deferoxamine (DFO,) can reduce tissue damage from experimental stroke by 50% (one dose, delivered following stroke). More importantly, IN DFO can reduce tissue damage following stroke by 65% when administered 48 hours prior to stroke (preconditioning). Recently, IN administration of mesenchymal stem cells significantly decreased the behavioral deficits and immunocytochemical indicators of PD in rats. IN administration of neuroprotective or neuroregenerative compounds or cells may be effective in the prevention and treatment of combat-related disorders.

2. Traumatic Brain Injury (TBI).

Our lab has developed and characterized models of TBI in large animals. We have models of concussion- and blast-induced TBI in pigs. Preliminary studies of blast-induced TBI demonstrated behavioral and cardiovascular changes followingTBI. Concussive TBI yields a significant increase in intracranial pressure that is amenable to treatment. The long-term goal of these projects in swine is to develop therapeutics that can be administered IN for the treatment of TBI.

Overall goals—Prevention and Treatment—Research for the Veteran

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Title: Direct Delivery of Neurotoxins to the Brain by an Intranasal Route
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Purpose of our proposal:

The men and women who served in the Persian Gulf Theater were exposed to a broad range of chemical and biological agents that may have affected the health of many veterans after the end of the Gulf War. Among the health complaints were immunological changes, autonomic nervous system changes, and development of neurological disorders. The studies of the current proposal will focus on the latter. The central premise of this proposal is that widespread misuse of pesticides led to signficant excess exposures, particularly to aerosolized compounds that can easily enter the nasal cavity. We hypothesize that some of these compounds (we will focus on DEET and permethrin) could reach the upper third of the nasal cavity, from which they can be directly delivered to the brain, causing tissue damage. This hypothesis is derived from the accumulating evidence for effective intranasal drug delivery.

Intranasal drug delivery provides an alternative, non-invasive method to directly target drugs to the central nervous system (CNS). This method allows drugs to be rapidly delivered to the CNS, even those that do not readily cross the BBB, which has prevented the use of many therapeutic agents for treating CNS disorders. However, just as therapeutic or beneficial agents can be delivered directly to the brain, compounds that might be neurotoxic can also follow the same route.

We proposed to intranasally administer DEET and permethrin to rats, first alone and then as a combination (or cocktail). Rats will be intranasally dosed weekly for 1, 2, 3, or 4 weeks and permitted to survive different periods of time, after which their brain will be sectioned and examined for ongoing as well as previous cellular injury. At a dose and survival time that yields tissue damage, another group of animals will be dosed and subjected to a battery of behavioral tests to assess either cognitive or motor impairment.

There are a number of animal models that have tried to mimic pesticide exposure in the Gulf War, and all entail either systemic or trans-dermal administration of individual pesticides or pesticide combinations followed by either histological evaluations of brain tissue or behavioral testing, or both. While these models are valid, they generally use high doses of pesticides so that delivery to brain is assured. The studies of the current propsal will use much smaller doses of pesticides, delivering them directly to the brain via the intranasal route. These studies are particularly important to troops currently deployed to the Persian Gulf because if toxicity is noted after intranasal administration, the specific pesticides used as well as the patterns of pesticide usage will have to be reassessed.

Results:
When anesthetized rats were dosed with intranasal DEET, they displayed simple motor seizures that were characterized by a motor arousal followed by a sudden, rapid emergence from anesthesia., making completion of the dosing difficult. While these seizures were easily recognized by the animal surgeon, they were not amenable to quantization. To quantify these seizures, we needed to obtain EEG's, and we do not have that capability. Another problem was that we were not able to obtain pharmaceutical or research grade DEET or permethrin. In order to properly conduct these studies, we need samples of DEET and premethrin in formulations that were used in the Gulf War. In conclusion, we detected a possible adverse effect from the intranasal administration of DEET.