

**The Nature and Causes of Gulf War Neurological
Syndrome and Gulf War-Associated Lou Gehrig's Disease
and the Need for Continued Funding for Research**

Testimony of

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As you know, for the past 10 years I have been leading a research effort at the University of Texas Southwestern Medical Center in Dallas to understand the illnesses that have affected many of the veterans who served in the 1991 Gulf War. Our thrust has been to try to cut through all the metaphysical debates about stress, plume models, and expert committee reports and get right to the heart of the problem: what is wrong with these veterans, what caused it, and how can we help them. This effort has carried us along a path of fascinating scientific studies to the brink of understanding the problem.

Right now I am encouraged at the progress that has been made in understanding the new type of brain cell damage that appears to underlie Gulf War veterans' symptoms. Up to a year or so ago, anyone who would give credence to anything other than stress as a cause of the problem was a pariah, but we are now seeing a broad change in viewpoint in the scientific community. Just last month I attended an NIH-sponsored meeting on responding to chemical terrorism, and the scientists in attendance were discussing the chronic brain effects of sarin nerve gas as a given. So the good news is that the bureaucratic resistance to research toward a biological explanation has finally been overcome, and the scientific world is poised to jump in and study the problem broadly. The bad news is that, just as clear directions are emerging for productive research to begin, funding for research on this problem has dried up.

Let me briefly list the main scientific breakthroughs that have been responsible for the change in scientific viewpoint. I'll discuss the evidence on three general questions: the nature of the Gulf War neurological illness, the causes of the Gulf War neurological illness, and the recognition of an elevated rate of ALS in Gulf War veterans. I will then discuss briefly a series of severe methodological errors in government-funded studies that are responsible for inconsistent findings.

The Nature of Gulf War Neurological Syndrome

First, we now know that down inside this mass of confusing symptoms that has baffled us for over a decade, there is at least one real disease—maybe two or three diseases, or one disease with several variants—that was caused by exposures in the Gulf War. Almost all of the varied symptoms relating to different body organs in this condition could be caused by damage to one organ—the brain. So what is the evidence that brain damage underlies this condition?

My group identified three symptom complexes that appear to be separate variants of a Gulf War neurological syndrome. Dr. Han Kan's team at VA has identified three symptom complexes that appear very similar to the ones we identified. In both studies the second symptom complex ("Syndrome 2") appears most like a neurological syndrome. We have completed several additional studies that show all three symptom complexes differ from healthy veterans on neurophysiologic and neuropsychological tests, suggesting a neurological basis. The most convincing evidence of a neurological basis for the syndromes comes from brain imaging studies of brain cell chemistry and neurophysiologic studies of the autonomic nervous system.

Evidence of brain cell damage underlying Gulf War neurological syndrome. In our studies comparing a well characterized group of sick Gulf War veterans and well control veterans, we measured the chemical composition of deep brain structures in the center of the brain, called the **basal ganglia**, with a well established brain chemistry test called Magnetic Resonance Spectroscopy, or MRS scanning. We found that the sick veterans had reduced levels of normal chemicals inside brain cells of the **basal ganglia**. This finding proves that the brain

cells in the **basal ganglia** of the veterans with this condition are physically damaged. Since we published this finding in 2000, two other independent research groups have made similar discoveries—Dr. Michael Weiner and colleagues at the UCSF medical school and the San Francisco VA Medical Center in 2001, and Dr. P. M. Menon and colleagues at the University of Mississippi Medical School and the Montgomery VA Medical Center in 2004, just last month. Dr. Weiner confirmed our finding of abnormal brain chemistry in the **basal ganglia**; whereas, Dr. Menon confirmed that finding and also found the same abnormality in the **hippocampus**. These “hard” scientific findings are giving us, and the rest of the scientific world, confidence that this is a real brain disease, and they are attracting more scientists to join in the investigation, which is what we will ultimately need to really bring help to the ill veterans.

Evidence of autonomic nervous system dysfunction. Another important path of research into the nature of the disease involves studies of the **autonomic nervous system**. This is what you might think of as the “automatic” nervous system, that part that is constantly carrying out all the automatic functions that you aren’t aware of, like digesting food, maintaining body temperature, heart rate, and energy level, and so on. The **autonomic nervous system** is very difficult to study, which helps explain why this problem has been so difficult for medicine to deal with. My group has a new study that will be published later in the summer that demonstrates a characteristic abnormality of the **autonomic nervous system** in ill Gulf War veterans compared with well controls. At least two other research groups have presented similar findings at scientific meetings, and these should be appearing in scientific journals later this year. These findings will go a long way toward explaining the symptoms that have seemed so mysterious up to now.

Followup survey to capitalize on these findings. For the past seven years my group has been proposing to do a nationwide survey in random samples of the deployed and nondeployed Gulf War-era military populations to compare the prevalence of the symptom complexes and neurological abnormalities in the two populations. In the telephone survey we will determine the prevalence of the symptom complexes and answer many questions posed by recent research. Then we will select random subsamples of the ill and well veterans, and bring them to Dallas for brain imaging, neurophysiologic tests and other sophisticated medical tests designed to explain the basis for the illness. We have Congressional funding for the survey, which is administered through USAMRMC at Ft. Detrick, and we are expecting to receive final clearance from the Ft. Detrick Human Subjects Research Review Board next week. This should allow us to start the pilot survey to test the methodology by late summer and to begin the survey by late fall, with results this time next year. In parallel with the survey, we will be advancing the brain imaging methods to be used in the later onsite medical testing phase. For this we are developing a state-of-the-art brain imaging center on the UT Southwestern Medical Center campus by adding the most advanced 3 Tesla brain imaging magnet with staffing to support it. Teams of neuroscience researchers are planning new brain imaging protocols to start testing later this summer.

Approaches to find treatments for the illness. At present no treatments are known to substantially relieve the symptoms of Gulf War neurological syndrome. Historically there have been two ways of finding new treatments for diseases, serendipitous discoveries by physicians treating patients and rational new drugs designed on the basis of scientific discoveries of how a disease works. The former is sometimes rapid but uncertain, while the latter is sure but may take

a long time. We are taking both approaches. Our national survey of Gulf War veterans will ask veterans if they have been treated with medications that are effective for them; if we are lucky, this could identify one or more effective treatments that are already available. Dr. Han Kang of VA is asking for this same information in his national survey which is currently in the field. In parallel we are studying the cellular and molecular basis of the disease so that in the future we, or others, will be better able to design new treatments with a higher likelihood of being effective.

Causes of Gulf War Neurological Syndrome

Proving that some environmental exposure causes a disease is a very difficult undertaking. It requires a combination of approaches with results all lining up to form a coherent picture. The usual approaches include epidemiologic studies showing statistical associations, genetic studies showing predisposition to illness from the exposure, and laboratory experiments that reproduce a similar illness in laboratory animals experimentally exposed to the causative agent. All of these have now been done for Gulf War neurological syndrome, and a coherent picture is emerging.

Epidemiologic Studies of Self-Reported Exposures. In my review of the published scientific literature, I count 15 epidemiologic studies in which the investigators asked large groups of veterans to report whether they recalled being in contact with a variety of possible causative exposures during the Gulf War (self-reported risk factors) and then analyzed to see which exposures were more strongly associated with chronic illness. Although these studies rely on veterans' recall of their exposures, two studies have examined the validity of these recall data and found that errors from inaccurate recall occur at the same rate in the ill and well groups, indicating that no bias results. The studies are remarkable in that they are consistent on one major finding. In the 10 studies that included questions on exposure to chemical nerve agents, all 10 showed that nerve agent exposure was more strongly associated with a case definition of Gulf War neurological syndrome than any other risk factor included. Thus, the body of epidemiologic studies nominates chemical nerve agent exposure as the most important cause of the illness.

Epidemiologic Studies of Geographical Location. Two epidemiologic studies have shown that military personnel deployed nearest the Kuwait-Saudi border during the conflict were at greater risk of later chronic illness. Our survey found very specifically that those personnel who were nearest the border area on the fourth day of the Air War (approximately January 19 and 20, 1991) have the highest risk of chronic Gulf War neurological syndrome. After discovering this association, we researched the dates of various exposures and found that January 19 and 20 was the exact period when Czech chemical weapons detection experts, working with the most sophisticated detection equipment, detected sarin in ambient air in the border area amid U.S. troop positions. Similarly, Dr. Lea Steele's survey of Gulf War veterans from Kansas found that personnel who were forward deployed during the conflict period had higher rates of Gulf War neurological syndrome. These findings add geographical and temporal specificity to the association with chemical nerve agent.

Studies of Genetic Predisposition. In one of our earlier studies, we reasoned that if

repetitive exposure to low-level sarin was the cause of the Gulf War neurological syndrome, then personnel born with low resistance to sarin would be the most seriously affected with chronic symptoms. Through searching the scientific literature, we identified a gene—the PON1 gene—that codes for a blood enzyme—type Q paraoxonase—that destroys chemical nerve agents in the bloodstream before they can get to the brain and cause damage. So we tested out theory by measuring the blood activity of the paraoxonase enzyme in groups of ill and well Gulf War veterans. As you know, we found that the veterans sick with Gulf War neurological syndrome had been born with low levels of type Q paraoxonase, meaning less protection; while those who remained well had been born with high levels, more protection. This was a remarkable finding, because type Q paraoxonase essentially has only one toxicologic function, and that is destroying nerve agents like sarin, soman and VX, but it doesn't very strongly attack any other chemical toxin. Taken altogether, this set of findings strongly connects Gulf War neurological syndrome directly to nerve agent exposure, further pointing to a link with sarin exposure.

Animal Model Experiments. Back in 1995 during our initial epidemiologic studies, Dr. Tom Kurt of my research group designed a set of animal experiments to test the biological plausibility of our epidemiologic findings, and with funding from the Perot Foundation contracted with Dr. Abou-Donia at Duke University to perform the experiments. Those and later experiments by Dr. Abou-Donia showed that combinations of pesticides, insect repellants, and chemical nerve agents can cause permanent damage to nerve cells in the brains of experimental laboratory animals. Following publication of those findings, there has been a crescendo of laboratory animal experiments by researchers throughout the country and overseas, adding to our knowledge of the long-term brain affects from low-level, repetitive exposure to these chemicals.

A longstanding criticism of this body of research was that the experimental conditions in the laboratory did not closely enough fit the exposure situation of military personnel in the 1991 Gulf War. Indeed, in their 2000 report *Gulf War and Health Volume 1: Depleted Uranium, Pyridostigmine Bromide, Sarin, Vaccines*, the Institute of Medicine's Committee on Health Effects Associated with Exposures During the Gulf War concluded that, whereas there is sufficient evidence to conclude that exposure to sarin at levels sufficient to cause immediate symptoms of toxicity can lead to chronic brain damage, they found insufficient evidence to conclude that exposures below symptomatic threshold could cause chronic damage, and they called for more animal experiments to fill this research void.

This issue was finally addressed in three scientific publications that appeared in October 2002 by Dr. Rogene Henderson of the Lovelace Respiratory Research Laboratory, University of New Mexico, and collaborators at the U.S. Army Medical Institute of Chemical Defense in Aberdeen, Maryland. Their experiments exposed rats to sarin by inhalation for 5 or 10 days, with and without heat stress, at doses of sarin below the levels that would cause signs of immediate toxicity. Throughout the dosing period they monitored breathing, body temperature and activity level—the main indicators of immediate sarin toxicity in rats—and found no immediate effects. They also sacrificed half the animals immediately after the end of the dosing period to examine the brains which were found to be entirely normal. These findings thus satisfied the IOM Committee's stipulation of no evidence of immediate toxicity. Then 30 days after the end of the sarin exposures, they sacrificed the rest of the rats, examined their brains and found striking evidence of structural damage to **cholinergic receptors** in several deep brain structures, including the **basal ganglia** and **hippocampus**. Recall that the MRS scanning studies, discussed above, found biochemical abnormalities in the **basal ganglia** and

hippocampus areas of veterans ill with Gulf War neurological syndrome. In a second paper in the series, the investigators presented evidence of damage to the **autonomic nervous system** caused by the sarin exposures. Consequently, the laboratory animal experiments of Henderson and colleagues, which satisfied the IOM Committee's requirement to simulate exposure conditions present in the 1991 Gulf War with exposure levels that produced no signs of immediate toxicity, identified sarin-induced damage to **cholinergic receptors** in the very brain regions found to be biochemically abnormal in the ill veterans—the **basal ganglia** and **hippocampus**—and damage to the **autonomic nervous system** also being found to be functioning abnormally in ill veterans.

Extension of Human Studies to Link to the Findings of the Animal Experiments.

My group is presently completing the analysis of a complex human experiment where we performed brain scans measuring brain bloodflow throughout the brain with the SPECT method (single photon emission computed tomography). We performed two resting SPECT brain scans on each of 23 veterans with Gulf War neurological syndrome and 17 well veteran controls. The first scan was performed while the subjects were receiving an intravenous infusion of saline (a placebo), and the second scan 48 hours later while they were receiving an intravenous infusion of physostigmine, a safe drug that stimulates **cholinergic receptors**, the ones found to be damaged in Henderson's sarin-exposed rats. Our prediction was that, if sarin exposure caused the veterans' illness, certain parts of their brains would respond less well to the physostigmine infusion. Moreover, of the three syndrome variants only syndrome variant number 2 was linked epidemiologically with sarin exposure; consequently, we predicted that this subgroup would show the most abnormal response to the cholinergic stimulus. If our analysis were to confirm these predictions, it would link the objective abnormalities of ill Gulf War veterans directly to the mechanisms of sarin-induced brain cell damage identified in Henderson's animal model. We expect to complete these analyses and submit a scientific paper for later publication this year.

Discovery of the Excess Rate of Lou Gehrig's Disease in Gulf War Veterans

In late 1997 I began a collaboration with Major Michael Donnelly and members of his extended family to investigate whether the rate of occurrence of Lou Gehrig's disease (amyotrophic lateral sclerosis, ALS, motor neuron disease, MND) was greater than expected in young Gulf War veterans, less than 45 years of age. Major Donnelly flew jet fighters in combat missions during the 1991 Gulf War and six years later developed ALS at age 42. Within months of starting to look for additional cases, we had identified 17 young Gulf War veterans with ALS. My epidemiologic calculations confirmed that this was over twice the rate expected when the incidence rate of ALS of the U.S. population in each one-year age group is applied to the numbers of Gulf War veterans in the same age groups. This calculation is a time-honored method resulting in the standardized morbidity ratio (SMR) statistic. In addition, I constructed the "epidemic curve," a graph showing the number of cases diagnosed in each year since the 1991 Gulf War. The epidemic curve showed an average of one case per year in 1991 through 1994, exactly the expected number, and thereafter two in 1995, three in 1996 and 1997 and five in 1998. The combined number in 1995-1998 was 2.3 times the expected number, and the number in 1998 was 3.2 times greater than expected. These differences were statistically significant, thus not due to chance. This finding suggested that in the final year of our study, the

rate of ALS cases was still increasing and could herald a serious emerging public health crisis in future years.

While attempting to publish the controversial finding in a medical journal, I approached the VA Central Office to collaborate by providing me the names of all Gulf War-era veterans with ALS from their nationwide computer records so that I could confirm them and add them to my case series for a more complete study. When the VA administration declined, I asked that they at least send a letter to all ALS patients apprising them of my study, but this too they declined. However, they immediately set up a VA-supported study to check my findings. In 2001 I presented the results of my study to the new VA Secretary Anthony Principi and suggested that he check my findings against those of the VA study still in progress and, if the results were mutually confirming, to consider service-connecting the Gulf War veterans with ALS. Six months later Secretary Principi announced this decision.

Because of the extreme skepticism of our finding among neurologists generally, my paper met stiff opposition by journal peer reviewers and was not published for several years. Finally when the VA study was completed, showing essentially the same result, both papers were published together in the September 2003 issue of the journal *Neurology*. Subsequently, the VA established a center for the study of ALS at Duke University, where the subsequent course of the problem is being monitored. Skepticism of the finding continues to be expressed by some neurologists, with one negative editorial and a critical letter to the editor. The findings of the Duke ALS Center, however, should clarify the nature and full magnitude of the problem shortly.

New funding for ALS breakthrough research. Another important outcome of the finding was that it stimulated a new funding initiative for innovative research into the causes and treatment of ALS, sponsored jointly by VA, the National Institute for Neurological Disorders and Stroke (NINDS) of NIH, and the private ALS Association (ALSA). Shortly after VA Secretary Principi announced service-connection of the Gulf War veterans with ALS, representatives of the three institutions began meeting to plan a research response to the problem. In late 1993 NINDS released a request for applications (RFA) for an R21 grant offering—the R21 mechanism encourages high risk, innovative proposals to stimulate breakthroughs in the understanding of the disease. Expecting only a dozen or so applications, NINDS officials were surprised to receive over 70 research applications, a huge outpouring of interest in the disease. After peer review of the applications by an NIH study section, several projects were funded; however, before all the awards were made VA scaled back its contribution to the consortium, and fewer projects will now be funded.

Hypothesized explanation for the increased rate of ALS in Gulf War veterans. As for the cause of the increased rate of ALS in Gulf War veterans, there is insufficient evidence to reach a conclusion at present; however, existing evidence gives important clues to the causal mechanisms. First, it is clear that ALS has a strong genetic basis. Approximately 10% of civilian ALS cases are familial, and approximately half of these are associated with an identified set of gene mutations in the SOD1 gene. Second, many epidemiologic studies of civilian ALS have shown links with environmental exposures. One of the most interesting is a strong association with farming occupations and with long-term exposure to pesticides and herbicides; recall that most pesticides used in farming are organophosphate chemicals in the same chemical family and with the same mechanism of action as the chemical warfare nerve agents sarin, soman and VX. Third, in our study of ALS in young Gulf War veterans we found that 66% of our ALS

patients had symptoms of Gulf War neurological syndrome beginning during, or soon after returning from, the 1991 Gulf War and developed the first symptoms and signs of ALS five to eight years later. Since only about 15% or so of Gulf War veterans in general developed Gulf War neurological syndrome, finding that 66% of the ALS patients had it long before the onset of their ALS suggests a link between the two diseases.

These findings could be explained by the hypothesis that widespread exposure to low-level sarin in the Gulf War caused both chronic neurological diseases: 1) Gulf War neurological syndrome due to brain cell damage in the approximately 15% of troops born with low levels of type Q paraoxonase, and 2) ALS in the much rarer individuals who were genetically susceptible to getting ALS (through as yet undiscovered genetic mutations like those in the SOD1 gene). Thus, it is possible that the young veterans who got ALS might have gotten it anyway, but at a much older age, namely, in their 60s and 70s, but Gulf War exposure to low-level sarin nerve agent—a far more potent environmental toxin—accelerated the appearance of ALS by several decades. Again, let me emphasize that this is an unproven hypothesis that would explain the facts we have, but we have insufficient evidence at present to confirm it.

Inconsistent Findings from VA and DoD Research from Plume Models, Hospitalization and Mortality

In assessing the evidence on the nature and causes of Gulf War neurological syndrome, one must account for the seemingly contradictory, though inconsistent, findings of a number of epidemiologic studies performed by researchers in DoD and VA as well as those performed by researchers at Kings College London, funded in early years by DoD.

The first set of studies, published in the 1996 time frame, showed that the deployed population had no higher rates of hospitalization in military hospitals and no higher mortality rates than the non-deployed Gulf War-era population. Actually, the mortality study showed significantly excess mortality rates from motor vehicle accidents in the deployed population, although this important finding has repeatedly been obscured in dissemination of the findings. A second set of DoD and VA studies, published several years later, similarly used hospitalization and mortality rates as surrogate measures for Gulf War neurological syndrome to test for an association with exposure to low-level nerve agent. In the second set, however, DoD researchers attempted to correct some of the negative bias by counting hospitalizations in VA hospitalization databases. This made a bid differences in the results.

The first set of studies showed no increase in hospitalization or mortality in Gulf War veterans exposed to the 1997 Khamisiyah plume, generated by DoD's plume modeling. The second set, with VA hospitalizations included, showed increased rates of hospitalization associated with deployment and with the 2000 Khamisiyah plume, but these important corrections on earlier findings have been obscured in dissemination of the findings.

All of these studies suffered from serious methodological flaws that minimized or entirely obscured strong adverse health effect of deployment. The major flaws are as follows:

Use of deployment as a surrogate for a case definition of Gulf War neurological syndrome obscures the health effects of deployment. The studies that compared the rates of hospitalization or mortality in the deployed versus the nondeployed Gulf War-era military population were using deployment as a surrogate measure for illness. Since, however, only a relatively small percentage of the deployed became chronically ill, the studies obscured the

associations with the illness by grouping the small number of deployed veterans who became ill with the much larger number of deployed who did not become ill and comparing the combined group to the nondeployed population. This averaging of the ill veterans with the larger population of well Gulf War veterans made it all but impossible to see the effects of the illness.

Use of hospitalization and mortality as surrogates for a case definition obscures the health effects of deployment. A fundamental feature of the Gulf War neurological syndrome is that the ill veterans have disturbing symptoms but no clinically evident signs of known diseases. Consequently, physicians do not tend to hospitalize Gulf War veterans for this problem, and it does not progress to a fatal outcome, except in motor vehicle accidents. Consequently, rates of hospitalization and mortality are not appropriate measures of the disease, and studies using them to test the association of the illness to deployment or plume exposure are foreordained to show negative results.

Studies measuring outcomes in military hospital records only are strongly biased against finding an association with Gulf War neurological syndrome. In the first several years after the 1991 Gulf War, the U.S. Military was severely downsized, resulting in separation of large numbers of active duty personnel. Many personnel who returned from the Gulf War with chronic illness that impaired their performance either left the service voluntarily or were “downsized” out, as personnel better able to perform were preferentially retained. Evidence of this selective attrition of those returning ill from the war was published in the first DoD hospitalization study. Since military personnel are no longer eligible to be admitted to military hospitals after leaving active duty, the selective attrition of the sickest personnel soon after the war produced a severe selection bias in studies relying only on military hospital records. Such studies were strongly biased toward finding no association between deployment and hospitalization, or conditions diagnosed with ICD-9 codes in hospitals.

Studies using nonspecific definitions of Gulf War neurological syndrome are biased toward finding negative results. Early in the history of Gulf War illness research, around 1993, a decision was made in the government to the effect that “there is no Gulf War syndrome,” and this led to pressure on researchers who wanted government funding not to use a case definition of the illness in their research. Without at least a provisional case definition, however, it is virtually impossible to design studies that will elucidate the nature of the illness, or illnesses, and connect them with causes. This unfortunate government decision is arguably the main reason for the delay in progress in this research field. Finally, when a few studies bucked the policy and used provisional case definitions successfully to make promising discoveries, research groups that had performed expensive population surveys without a case definition in mind attempted either to prove that no case definition was possible or to concoct case definitions after the fact from data collected earlier, even when the collected data were insufficient for defining a case definition.

The most important example of the unproductive use of a nonspecific case definition concocted after the fact was the series of studies from the Kings College London group. In place of a case definition describing the disease that veterans were complaining of, they defined Gulf War illness as having a score of greater than 72.2 on the SF-36 questionnaire, which measures functional impairment regardless of the cause. This case definition essentially counted veterans as having Gulf War illness if they had any condition that caused them to feel bad. Consequently, many veterans with diseases other than Gulf War neurological syndrome that made them feel

bad were mistakenly counted as cases, and conversely, many with typical symptoms of Gulf War neurological syndrome but who were not very ill with it were not counted as cases. This severe degree of bidirectional misclassification has caused all studies from the Kings College London group to reach spuriously negative conclusions.

Studies using nonspecific measures of nerve agent exposure are biased toward finding negative results. With the high likelihood of low-level nerve agent exposure playing a causative role in the chronic illnesses of Gulf War veterans, it was crucial to develop accurate measures of low-level nerve agent exposure for epidemiologic studies. Inaccurate measures of the exposures would predictably bias studies toward finding no association with illness. Four types of measures of low-level nerve agent exposure have been used in studies: 1) mathematical models of the plume generated by demolition of the CW-containing ammunition depots at Khamisiyah and other sites in Southern Iraq, 2) veterans' self reports of having actually seen the explosion of the ammunition depot at Khamisiyah, 3) veterans' self-reports of low-level nerve agent exposure at any time or place during the war, and 4) epidemiologic linkage of illness with low type Q paraoxonase, a blood enzyme that selectively protects from nerve agent.

Studies using measures of low-level nerve agent of types 2, 3 and 4 have rather consistently found strong associations between low-level nerve agent exposure and Gulf War neurological syndrome; whereas, all studies using measures of type 1, plume modeling, have shown no association, except for an association with one hospital diagnosis, cardiac arrhythmias, in the latest hospitalization study. Although the researchers who used plume-modeled markers of nerve agent exposure have argued that this measure is preferred because it is objective and not reliant on veterans' self reports, I consider the exposure measures from plume modeling spurious for the following four reasons.

First, the plume models attempt to express only the sarin exposure that resulted from post-war demolition of ammunition depots and do not attempt to capture the more apparent, and widespread, nerve agent exposures that occurred during the Air and Ground War phases of the 1991 Gulf War conflict. These exposures were documented by widespread sounding of nerve gas alarms among our troop concentrations, simultaneous nerve agent detections by Czech CW experts among our troop concentrations, and scrupulous review of exposure records by credible nongovernment experts. The plume models also did not include exposures that may have occurred after the war to personnel who ventured into nerve agent-contaminated sites or handled vehicles or equipment contaminated at the sites. By thus failing to include these exposures, which are captured by the other three approaches, the plume models captured only one component—most likely a minor component—of the true exposure burden. Consequently, the plume models misclassified many personnel as not exposed who really were exposed earlier during the Air and Ground War phases of the conflict or later during the cleanup operations.

Second, the plume models used many input parameters of low reliability, thus yielding models with a great variance.

Third, the plume models themselves were never submitted for scientific publication through the peer review system of respected scientific journals.

Fourth, in the midst of controversy over the plume models, DoD officials at OSAGWI transmitted to VA a computer database containing flags of plume exposure from the 1997 plume and from the 2000 plume. When VA officials cross-tabulated the two flags they found irregularities in the death rates suggesting that the 2000 plume may have been manipulated invalidly to exclude deceased veterans from the 2000 model's plume-exposed group. A VA report attempting to explain the discrepancy was, in my view, not cogent.

Combined effects of several methodologic flaws in the same study. The confusion produced by studies containing such flaws is compounded by the fact that some of the government-funded studies contained more than one of the methodologic flaws described above. For example, one study measured nerve agent exposure with a flawed plume model that misclassified veterans on the exposure, measured the illness outcome with hospitalization diagnoses that did not detect Gulf War neurological syndrome, and restricted the hospitalizations counted to those from military hospitals that excluded the sickest personnel who left the military shortly after the war. Such studies provide no useful information and yet have been widely quoted and have exerted strong influence on government policy. It is my observation that these, and other less obvious, methodologic flaws are responsible for the inconsistent evidence against the existence of a Gulf War neurological syndrome and against the role of nerve agent exposure.

Conclusions

Over the past several years published research from diverse institutions has provided evidence from which we can begin to understand the nature and causes of the unusually large burden of illness in veterans of the 1991 Gulf War. The evidence increasingly suggests that there are at least two serious disease problems in this population, a very common condition that I refer to as the Gulf War neurological syndrome and an excess rate of the rare condition ALS. Although not covered in this review, there is also increasingly compelling evidence of excess rates of birth defects. There may be other diseases emerging in this population; for example, with two environmental diseases affecting the brain already documented, it would not be unexpected to see an excess of brain tumors or other cancers, as we reach the end of the expected latent period when cancers would be expected to appear.

The weight of the evidence also points increasingly to exposure to low-level sarin nerve agent as a predominant player, perhaps potentiated by other environmental co-exposures, in the causal mix. Before the Gulf War U.S. chemical defense doctrine held that exposure to low-level nerve agent did not lead to chronic effects, and for over 10 years after the war, false confidence in this doctrine served as an impediment to scientific research into its role in Gulf War veterans' illnesses. We now know that the old doctrine was based on overly simplistic studies of single exposure events and insensitive measures of chronic brain effects. Current evidence clearly shows that repetitive, low-level nerve agent exposures, at doses too low to cause immediate symptoms of toxicity, regularly lead to chronic brain changes in vital deep brain structures and related chronic, disabling symptoms.

The good news from this is that we have learned much and are on the verge of scientific breakthroughs that would lead to treatment of the ill veterans and prevention of brain injury from nerve agent exposures in the future. The bad news is that we do not yet have a treatment for the tens of thousands of ill Gulf War veterans, and government funding for further research to capitalize on emerging breakthroughs has all but dried up. Even limited funding that is supposed to be going to new research on Gulf War neurological syndrome and ALS is being quietly reprogrammed to other uses.

Now is the time to invest in a new wave of research funding for these important questions. Riding the crest of recent research breakthroughs, a new round of research funding is now well timed to translate the new findings into practical treatment and prevention products. Once funded, we must then ensure that the funding actually gets to our best researchers who will

avoid the pitfalls of the past decade and use the resources to advance understanding to a higher plane. The public-private consortium of NINDS, VA and ALSA to fund high risk, breakthrough research on ALS is a model for this new wave of funding, although the pullback of VA funds illustrates the bureaucratic hurdles that will have to be overcome. The recent funding alliance between NINDS and the U.S. Army Medical Institute of Chemical Defense to create a new extramural grant program for research into defense of chemical terrorist threats is another good model that should be supported.

The most optimistic development is the growing awareness in the scientific community of the legitimacy of research into the chronic brain effects of low-level chemical exposures. Resulting from a decade of solid research published in reputable scientific journals, this broad awareness will gradually stimulate wider interest among our best scientists and simultaneously wear down the bureaucrats who would hold back progress. Now is the time to put resources into solving this problem for the relief of Gulf War veterans and the protection of future military personnel and civilians who may be exposed to these chemical threats.

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