

## Gulf Related Illness - Current Perspectives

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**SUMMARY:** In the years after Operation Desert Storm and Operation Granby, some 4-8% of veterans of the conflict began to report symptoms of illness. Common complaints included fatigue, impaired cognition, joint pain, sleep disturbances, and chest pains. Between 1992 and 1994 in the USA, and later in the UK, governments set up medical assessment programmes to define the scope of the problem in qualitative and quantitative terms. Initial efforts moved to extensive epidemiological assessment and a search for causative mechanisms of what became termed "Gulf War Syndrome". Eventually significant sums of money were invested in medical and investigative research in an attempt to relate symptoms to causes.

This paper presents the historical background and context to the problem of Gulf and war related illnesses, summarises the findings of relevant epidemiological studies and discusses some of the hypotheses that have been generated to explain the clusters of symptoms reported by veterans. Finally, the current UK research programme and its underlying rationale is presented. The aim is to provide an overview of the current position and assist in the interpretation of a diagnostically difficult area.

### Historical Background

Kuwait was invaded on the 2nd of August 1990 by 100,000 Iraqi troops and after the failure of political manoeuvres to secure their withdrawal, Operations Desert Storm (US) and Granby (UK) were launched by Allied Forces on the 17th January 1991. More than 1 million personnel from over 30 countries were deployed, the greater part of whom were from the USA (697,000), Saudi Arabia (118,000), UK (51,000), UAE (40,000), Egypt (40,000), and Oman (25,500). France, Syria and Kuwait were also significant contributors. Air superiority was achieved early and Iraqi Forces were driven out of Kuwait by ground forces in a short offensive lasting from February 24th to 28th. Operations were largely completed within 6 weeks and most troops were withdrawn from the Gulf region by mid-1991.

In the year after their return from the Gulf personnel in several nations, but predominantly the USA, reported a variety of illnesses which had as their common denominator service in the Gulf during Operation Desert Storm. Following a television programme in the UK in June 1993 similar reports of illnesses surfaced here. In July 1993 the then Minister of the Armed Forces invited any veterans who believed they were suffering from unexplained symptoms to write to him personally. Shortly after this the Medical Assessment Programme (MAP) based at RAF Wroughton was established to act as a specialised unit to assess UK personnel who were suffering similarly. Canada and Denmark have instituted similar programmes.

In the USA several separate programmes were established between 1992 and 1994 under the auspices of the Department of Veterans Affairs (DVA) for ex-service personnel (Persian Gulf Health Registry Examination Program (PGHREP) and the Department of Defence for serving members of the Armed Forces (Comprehensive Clinical Evaluation PROGRAM (CCEP)). Of the nearly 700,000 US personnel in the Gulf some 62,000 (9%) have registered in the PGHREP and 34,000 (5%) in the CCEP. Of these around 11-12% have no significant health problems and within the CCEP around 20% have deferred any medical assessment until later. These numbers compare with some 4% of the UK personnel who served in the Gulf and who have registered in the MAP.

The initial thrust of all investigations, within all affected nations, was directed at defining the scope of the problem in both quantitative and qualitative terms. The aims were to provide specialised programmes which could assess the nature of the symptoms reported by veterans and provide support. The extent and nature of these programmes differed markedly between nations with the USA investing the greatest proportion

of resources. As the scale of the problem became apparent, the focus of investigation moved to epidemiological investigations and in the USA in particular several expert committees were set up in 1993 and 1994. These were followed by the Presidential Advisory Committee on Gulf Veterans Illness (PAC) in May 1995. Until this time, no co-ordinated scientific investigation of the illnesses had taken place, although in FY96 a total of \$37M was spent by the DVA, DoD and Health Departments on 91 different projects. The Persian Gulf Veterans Co-ordinating Board (PGVCB) now co-ordinates these studies however, it is worth noting that 61 of the 91 studies are epidemiological with the primary objective of determining the frequency of selected signs and symptoms and any association with specific exposure factors. Only 18 studies are focused on basic research with the effects of multiple exposure to organophosphorus compounds and carbamates, chemical weapons and infectious diseases, depleted uranium (DU) and stress dominating.

In the UK, no research of any kind was funded until 1996 when MOD undertook to fund two epidemiological studies approved by the Medical Research Council. These studies are investigating the health of veterans and their children (London School of Tropical Hygiene and Medicine under Dr Patricia Doyle; University of Manchester under Professor Nicola Cherry). The former study specifically addresses reproductive health outcomes in UK Gulf veterans and the latter the general health status of UK veterans who served in the Gulf. Also within the UK, but funded by the US DoD, a study which compared the health of Gulf Veterans with their contemporaries in Bosnia and those not deployed, was undertaken at the Gulf War Illness Research Unit, Guy's, King's and St Thomas's Medical School, London. An additional study was commissioned in 1998, by the MoD, at the University of Wales Medical School, Cardiff under Professor Glyn Lewis to undertake a systematic literature review of worldwide published research relating to Gulf veterans illnesses.

With the election of the new Government a new policy statement 'Gulf Veterans' Illness: A New Beginning', was published in July 1997 and provided the funding for a new research programme. This was the first funded experimental study to address the consequences of the administration of the pretreatment drug pyridostigmine bromide (PB) and the 10 vaccines administered during the Gulf conflict. The major proportion of research funding however has been committed by the US government and at the time of writing this exceeds \$115M, with the probability that more will be allocated within the coming financial year.

## Post-War Syndromes

Diagnostic criteria, and the fashion for certain disease patterns, change with time and between countries. Even today with the internationalisation of diagnostic criteria (currently ICD-10) consensus frequently only occurs where there is defined pathology. When one enters the realms of symptomatology of physical pain, malaise and illness particularly when there may be a psychological component to the illness, there is much disagreement within countries and indeed between specialities. Modern trends within developed nations tend to the “medicalisation” of patterns of relatively frequent symptoms into “syndromes” which may have no readily identifiable organic cause but which, none the less, are real to those that suffer.

Despite these historical and cultural differences there have been, nevertheless, unexplained and diagnostically difficult illnesses recorded in war veterans since the American Civil War (1861-1865) (1). The names of these syndromes differ although there is a remarkable degree of commonality in the recorded symptoms (Table 1). The list is by no means exhaustive and highlights five of the most frequent symptoms and signs. In the majority of cases diagnoses are made on the basis of self reported signs and symptoms, ill-defined diagnostic criteria, little certainty over cause and most importantly for the patients, no established treatment regime.

The regular appearance of these clusters of symptoms, and their clinical manifestations in different guises, have been a characteristic feature of 20th century medicine. They commonly include chronic fatigue or lassitude, impaired cognition (with the associated problems of poor attention span and memory), arthralgia and/or myalgia, sleep disturbances, headache and/or dizziness, nausea, chest pain and shortness of breath. The clusters and combinations vary. A common characteristic is that when groups of people associate, causes are sought for the condition which leads to postulation of “syndromes” which are frequently associated with putative exposure to environmental conditions/contaminants. In most of these “clusters” there is usually little evidence of exclusive cause-effect or dose-effect relationships. Examples include sheep dippers, illnesses, multiple chemical sensitivity, sick building syndrome, fibromyalgia (FM), chronic fatigue, and post-viral syndromes. The terminology used to define these syndromes often reflects the medical speciality of the originator although the descriptors frequently overlap similar clusters of symptoms in “syndromes” defined by others.

**Table 1**  
**Names and some commonly reported symptoms of Post-War Syndromes**

Syndrome name	Symptom				
	Fatigue/ Exhaustion	Shortness of breath	Headache	Muscle/ joint pain	Sleep/ memory disruption
Da Costa Syndrome (US Civil War)	+	+	+		+
Battle fatigue/ Shell Shock/ Effort syndrome (WW1)	+	+	+		+
Effort Syndrome Acute Combat Stress Reaction (WW2)	+	+	+		+
Post-Vietnam Syndrome/PSTD (Vietnam War)	+	+	+	+	+
Gulf War Illness	+	+	+	+	+

## Is there a “Gulf War Syndrome”

There have been many epidemiological studies conducted on Gulf veterans within the USA and there are currently several on-going studies which are addressing specific aspects such as birth defects and cancer incidences. Many studies have already reported (2,3,4) and some remain the subject of much debate on statistical methodology and interpretation (5).

Surveys of mortality and hospitalisation data have found no convincing evidence of increased rates of hospitalisations in the 4 year and 8 month post-war period (4, 6) in Gulf deployed, active duty personnel compared with those not deployed. Of statistical significance in two studies were higher rates of death from unintentional injury (motor vehicle and aircraft accidents) in Gulf veterans (2,3). The implications of this finding is the cause of much unresolved debate.

Preliminary results from reproductive outcomes studies suggest little evidence of higher risks of birth defects though the sample sizes are small. The ongoing study by Patricia Doyle will address these issues in UK veterans.

There have been many studies of self-reported symptoms of deployed and non-deployed veterans within the USA. The quality of these studies has been variable, however the most robust US studies (7,8) found a significantly higher prevalence of certain symptoms which persisted for longer than 6 months e.g. fatigue, joint pain, nasal congestion, difficulty remembering, muscle pains, headache. These and other studies suffer from the possibility that there was bias towards the selection of persons with symptoms as well as the limited numbers of veterans studied.

A study of over 1000 self-selected UK veterans in the MoD MAP study has reported this year (9). The evaluation included a questionnaire to establish exposures (if any), a comprehensive medical history, physical examination and laboratory investigations. The medical symptoms reported were similar in type and incidence to that seen in the US surveys and included fatigue, joint and muscle pains, cognitive problems, headaches and respiratory disorders and altered sleep patterns amongst others.

The most comprehensive and robust study reported to date is that of Wessely’s group in the UK (10,11). This study was again questionnaire based but with a rigorously controlled, cross sectional design stratified for age, rank and several other possible confounders. There were three study groups, each containing approximately 4,250 individuals: Gulf War cohort, Bosnia cohort and a third cohort of servicemen serving during the Gulf War but not deployed to the Gulf. The response rates were high (>65%). It was apparent that the perception of physical health and ability was significantly worse in the Gulf War cohort than in the other cohorts even after adjustment for confounders. The most distinguishing feature of this study however was the consistency of the elevated incidence of reported symptoms in the Gulf cohort. Within this group the incidence of reported signs was approximately double that of both other groups in virtually all symptoms reported, even those which occurred with low frequency. Those with the highest frequency included substantial fatigue, symptoms of post traumatic stress disorder (PTSD), and other psychological disorders.

The conclusions from these studies suggest a familiar pattern of ill health associated with exposure to adverse events and evidence for this was found in all of the cohorts of the UK study. The authors suggest that these features are not unique or causally implicated in Gulf related illness. However there was some limited evidence of a linkage to the vaccination programme. Statistical analysis of the results from this study (11) using factors analysis, concluded that three factors in the

Gulf war cohort (symptoms associated with mood, respiratory system and peripheral nervous system) accounted for only around 20% of the variance. The implication of these findings is that the three selected factors do not account adequately for the correlations amongst symptoms in UK servicemen deployed to the Gulf and indicates that there is no statistical evidence for a group of symptoms that can be called a syndrome.

**Hypotheses and research upon “Gulf War Syndrome”**

An underlying tenet of toxicology is that all substances are poisons; there is none which is not a poison; it is the right dose that differentiates a poison from a remedy (12). It is often possible to construct plausible hypotheses for the toxic action of a chemical or biological substance. What is considerably more difficult to obtain is a) robust evidence to establish its validity, and in particular, effects at dose levels to which humans are exposed and b) to link the proposed mechanism to the expression of a disease state in humans.

Some notable examples of success are Minimata disease which resulted from organomercury poisoning (13) and organophosphate induced delayed neurotoxicity (OPIDN) which occurred in an epidemic in the USA following the ingestion of an adulterated alcoholic extract of Jamaican ginger contaminated with tri-ortho tolyl phosphate (14). Much more difficult has been to establish cause and effect relationships between low doses of environmental contaminants and disease outcomes. Of current public concern for example are the

**Table 2**  
**Speculated causes of Gulf Related Illness**

<b>Pretreatment Regimes</b>
Pyridostigmine bromide (NAPS tablets)
Vaccines
Anthrax
Pertussis
Plague
Meningococcal meningitis
Typhoid
Cholera
Yellow fever
Poliomyelitis
Tetanus
Hepatitis B (selected medical personnel)
<b>Environmental contaminants</b>
Depleted uranium (DU)
Pesticides
Organophosphates e.g diazinon
Pyrethroids e.g. permethrin
Carbamates e.g. Propoxur
Insect repellent
DEET
Smoke from oil well fires
Petroleum products
Chemical warfare agents
<b>Diseases endemic to South West Asia</b>
e.g. Leishmaniasis
Sandfly fever
Malaria
Mycoplasma infections
<b>Physiological and psychological stress</b>

claimed hazards from electromagnetic radiation, pesticide and phthalate residues in food, fluoride in drinking water and particulate matter in the environment.

The speculated causes of “Gulf War Syndrome” are as diverse. In general, hypotheses for Gulf related illnesses focus upon the environmental differences (endemic disease, climate, pollution from oil fires), health regimes (medical treatment/pretreatments, public health measures e.g., pesticide and insect repellent usage, diet and drinking), psychological and physical stress, and battlefield hazards e.g. exposure to chemical warfare agents, and depleted uranium (Table 2).

None of these materials or environmental factors, either alone or in combination, has ever been rigorously demonstrated to cause the symptoms reported by Gulf veterans at the dose levels to which they are believed to have been exposed. In general, hypotheses have been developed based upon the potential of combinations of drugs/environmental factors, such as a pesticide and an insect repellent whilst taking NAPS tablets, to induce adverse effects. Frequently the evidence produced draws upon effects produced at much higher dosages than might be reasonably expected in the field. An additional element of these hypotheses has been the concept of “overload” of physiological systems as a consequence of multiple interactive exposures to many different environmental contaminants.

Some current research topics (excluding epidemiological studies) funded by US agencies are listed in Table 3.

**Table 3**  
**Current US research topics investigating putative cause of Gulf related illnesses.**

Effects of pyridostigmine in rats differing in cholinergic sensitivity.
Butyryl cholinesterase genetic variations in persons with Gulf War Illness.
Effects of genetics and stress on neurobehavioural responses to pyridostigmine in rats.
Neurobehavioural and immunological toxicity of pyridostigmine, permethrin and DEET.
Low level sarin neurotoxicity and its modulation by pyridostigmine.
Sarin and pyridostigmine interaction under physical stress.
Strategy to identify non-additive response to chemical mixtures.
Evaluation of immunotoxicity due to concurrent exposure to DEET, pyridostigmine and JP-8 jet fuel.
Carcinogenicity of implanted depleted uranium fragments in rats.
Combat stress pharmacotherapy.
Antibiotic treatment of Gulf veterans’ illness.

Prior to 1997 no research was conducted in the UK upon the possible underlying causes of Gulf related illnesses. However in May of that year the UK government invited research proposals. The Gulf Veterans Illness Unit of the MoD was made responsible for commissioning the research and an Independent Panel of experts was appointed to oversee the work.

At the time of the invitation the combination of vaccines and pyridostigmine administered to UK personnel were regarded as the most favoured explanation of the illnesses. Proposals were invited which addressed this combination of treatments. CBD at Porton Down proposed a four part experimental study which was predicated on the worst case hypothesis: that if administration of combinations of vaccines and pyridostigmine could indeed produce adverse effects, then giving all vaccines

together with PB in a short period of time (analogous to that experienced by some personnel in the Gulf) would be most likely to show adverse effects. This approach would also allow the possibility that if such a combination did have adverse effects then it would be possible to focus down on to specific combinations, at a later stage, to identify the causative agents and study the mechanism of action.

From records of Gulf personnel it was established that the maximum number of vaccines that were administered during Operation Granby was 10 (Table 2). Anthrax was administered together with pertussis vaccine as an adjuvant to accelerate response time to protective immunity against anthrax toxin. The other anti-biological warfare vaccine administered was against plague (*Yersinia pestis*). Although conventionally labelled as anti-BW vaccines, they have no unusual characteristics that distinguish them from all other vaccines in terms of their formulation and concepts of use, apart from the use of pertussis vaccines as an adjuvant in adults.

The experimental design of the CBD studies, was to administer all vaccines within a six day time span to simulate the human vaccination programme. Unlike the situation during Operation Granby all booster doses of vaccines were also incorporated into the experimental design. PB was administered continuously for 28 days, from the 15th day after the first vaccination, by means of a sub-dermally implanted mini-osmotic pump.

The studies are being conducted initially in guinea pigs and subsequently in a small primate, the marmoset (*Callithrix jacchus*). In both species the maximum doses of vaccines are being selected to achieve an immune response which does not produce acute adverse effects that would prevent the animal from feeding and drinking. Doses of vaccine in excess of these levels might be life threatening as a consequence of the known acute effects of vaccines; this would prevent the studies addressing the longer term effects of multiple vaccinations. In the guinea pig study just completed the tolerable dose of vaccines was found to be 1/5th of the human dose of vaccine i.e., 1/5th of the volume of vaccine injected into humans. The dose of PB selected produces an inhibition of red blood cell acetylcholinesterase of approximately 30% (this is the target inhibition in humans to protect against poisoning by nerve agents).

The first phase of the investigation in guinea pigs was reported in June 1999 (15). The measured parameters of adverse effects included body weight, temperature, blood biochemistry and haematology, antibody titres against vaccines antigens, CD4<sup>+</sup> cells, CD8<sup>+</sup> lymphocyte and B lymphocyte numbers. There were small effects on bodyweight growth curves and animal temperature changes which generally correlated with procedures. In particular there were the expected transient changes in temperature associated with vaccine administration, although in the highest dosage group the body temperature remained slightly higher than the control groups throughout the study. In the highest dosage group there was a slight decrease in the rate of body weight gain of approximately 4.9%, this change was not statistically or clinically significant.

The next phase of this research programme will be in two parts. The first will be a replication of the guinea pig study design in the marmoset though using more sophisticated and complex measures of effects. Techniques of telemetric monitoring of physiological parameters, developed over many years at CBD, measures of EEG, ECG, EMG, cognitive behaviour, sleep, and grip strength in addition to measures used in the guinea pig study, will be undertaken in free ranging, socially mixed, home cage environments. Cognitive

performance will be assessed in trained marmosets using the CANTAB battery of testing procedures which have been developed for the assessment of neurodegenerative diseases in humans. Again the test procedures are conducted on a voluntary basis in their home cage environment using a stress free reward procedure. The overall aim is to remove the stress of a laboratory environment and experimental constraints totally from the testing environment.

The second part of the study is to be conducted at the National Institute of Biological Standards and Control (NIBSC). It was at this Institute in 1991 that it was reported that a combination of the anthrax and pertussis vaccines caused an adverse reaction in one strain of mouse (balb/c strain) but not in another (NIH strain). Concurrent studies at CAMR also did not show any adverse effects in the guinea pig. It was proposed that the NIBSC study be repeated with the additional complexity that a number of genetically different strains of mice be assessed. On this occasion with the full spectrum of vaccines administered during Operation Granby (not just the anthrax/pertussis combination) being given to the selected mouse strains. This study has the merit of assessing the "worst case" protocol in a third species but with genetic variants that might mimic the high degree of genetic diversity in the human population. In this way it may be possible to establish whether there are sub-populations within the human species that are uniquely sensitive to vaccines and PB combinations. This study is scheduled to commence in mid 2000.

A fourth study is already underway to assess the health status of employees at CBD who, for reasons of safety and visits to tropical climates, have been subject to vaccinations throughout their career. For ethical reasons the study will only address whether there are increased incidences of sickness and sick leave in this population and will only proceed further if unusual patterns are established and with the consent of staff within the study.

## Conclusions

Many veterans of the Gulf War suffer from a variety of symptoms and illnesses. Currently no evidence has been found for a definable "Gulf War Syndrome" although there is some evidence that the pattern of symptoms which occur in all serving and ex-serving members of the Armed Services occur at approximately twice the frequency in veterans of the Gulf War. The symptom clusters bear many resemblances to syndromes that have occurred after previous conflicts and to several current, diagnostically difficult conditions such as chronic fatigue syndrome and multiple chemical sensitivity. As in these illnesses, there are many hypotheses proposed to explain the conditions but there is, as yet, no scientifically robust evidence to explain the aetiology of the conditions. Significant research effort is now deployed with the USA and to some extent the UK to investigate some of these hypotheses and it is only within the coming 3-4 years that, hopefully, some meaningful explanations will be found. It is to be hoped that constructive and valuable treatment regimes will evolve from these findings to assist veterans in their current plight.

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