

Results of investigations on Gulf War veterans

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ABSTRACT – Investigations were undertaken on veterans of the Gulf conflict of 1990/91 at the Gulf Veterans' Medical Assessment Programme (GVMAP), to determine whether routine investigations should be carried out on these veterans. Blood investigations were analysed of a 10% random sample of veterans and also of two veteran groups – one group was well (asymptomatic) and the other unwell (post-traumatic stress disorder). Neurological investigations were carried out as well as 1,000 ultrasound studies and 3,000 ECGs. Almost all blood tests proved normal. The only significant differences found between the two groups were for the alanine/aspartate transaminase and gamma glutamyl transaminase values, where there were more abnormal findings in the unwell group. Abnormal, but expected, neurological investigations were found in those referred for these tests. Ultrasound abnormalities were related to known established clinical diagnoses, apart from three cases. ECG abnormalities were only present in those with known clinical diagnoses. It was concluded that reducing the number of investigations would not only be cost effective but should help to lessen veterans' anxieties.

KEY WORDS: Gulf War veterans 1990/91, implications, results, routine investigations, way forward

A short time after their return from the Gulf War of 1990/1, some veterans began to complain of symptoms of ill health, which became popularly known as

'Gulf War Syndrome'. There have been unsubstantiated claims in the media and by some veterans' activist groups that Gulf War service is linked to increased rates of mortality, birth defects, pregnancy problems and other more specific illnesses. Elsewhere claims of specific illnesses or unique syndromes have been made^{1,2} and carefully reviewed,^{3,4} finding little, if any, evidence of these links. In the UK, in response to these symptoms, the Ministry of Defence established in October 1993 the Gulf Veterans' Medical Assessment Programme (GVMAP), which was much heralded by the media. Similarly, in the USA, the Department for Veterans' Affairs Gulf Registry Health Examination Program (VA Registry) also started assessing veterans who had left the armed services in 1992. In 1994, the Department of Defense set up the Gulf veterans Comprehensive Clinical Evaluation Program (CCEP).

The GVMAP was never intended as a screening programme but, since it is the only programme available to Gulf veterans, it acted as a surrogate screening programme. Investigations were undertaken to help the medical assessments when it was thought that there may have been a condition specifically related to the Gulf War. Initial research,⁵⁻⁸ and that carried out later,^{9,10} benefiting from the results of almost a decade of research and assessment, found no evidence to support the concept of 'Gulf War Syndrome' or any unique Gulf War related illness. Similar conclusions have been reached at CCEP.¹¹ The diagnosis of 'symptoms, signs and ill defined conditions' (SSIDC) has now virtually disappeared in recent literature compared with earlier publications.^{9,10} Likewise, chronic fatigue syndrome is now rarely seen, as the well-established definition of this condition¹² is now applied.

The perceived potential health hazards of service in the Gulf were one or more of the following:^{4,7-10}

- use of insecticides or pesticides
- antibiological warfare vaccinations (anthrax with pertussis as adjuvant, plague)
- pyridostigmine bromide (NAPS)
- exposure to depleted uranium
- tropical diseases
- chemical warfare agents
- smoke and fumes from burning oil wells
- psychological stressors.

Key Points

The results of the majority of investigations carried out on Gulf War veterans were normal. Therefore the number of unnecessary, costly, potentially anxiety-provoking investigations should be reduced

The abnormalities found were mostly expected from known clinical diagnoses

Routine ECG and routine abdominal ultrasound investigations should be discontinued

The temptation to over-investigate should be resisted

After intensive research, with the exception of psychological stressors, none of the other above factors, singly or in combination, have thus far, with the possible exception of research by Cherry,^{13,14} been found to be the cause of ill health amongst Gulf War veterans.⁴ We therefore decided to review our investigation protocols. There have been unfounded suggestions that even more investigations should be undertaken on veterans irrespective of clinical indications.¹⁵ In this paper we will analyse the results of investigations carried out at GVMAP.

Methods

All Gulf War veterans who attended GVMAP received a full clinical assessment and a number of routine tests (Table 1). These routine tests were revised in November 2000 (Table 2). On clinical grounds any test indicated over and above those scheduled in either Table 1 or Table 2 were done irrespective of cost. Advice about these tests was obtained from the Royal College of Physicians in 1995 in the light of the then prevailing public and political pressures. However, it soon became clear that testing for leishmaniasis A and B was unnecessary, as no cases were found. This investigation was discontinued in 1996. On the basis of good clinical practice, lung function tests were no longer carried out routinely after September 1998. Routine chest X-rays were withdrawn in February 1999.

GVMAP has been variously located at RAF Wroughton Hospital, RAF Kelvin House (University College, London) and St Thomas' Hospital. Since May 2001, a peripheral clinic has been held at the Friarage Hospital, Northallerton. The laboratories undertaking these investigations have had different normal ranges and therefore all results have been analysed individually, according to the centre where the tests were undertaken. A normal test result is considered as one that is within the normal range set by the laboratory or one that is just outside the range but is of no clinical significance (ONCS).

Table 1. Routine tests undertaken at GVMAP before November 2000.

- Urine analysis: proteinuria, glucosuria, haematuria
- Full blood count and ESR
- Blood chemistry tests: urea, creatinine, electrolytes, liver function (AST/ALT, GGT), thyroid function, serum calcium and phosphate, alkaline phosphatase, C-reactive protein, creatine phosphokinase, glucose, immunoglobulins, serum protein electrophoresis
- Serology tests: amoebic indirect fluorescent antibody, borrelia (Lyme disease), brucella titres, complement fixation assay for coxiella, Epstein-Barr virus, cytomegalovirus, enterovirus screen and sandfly fever, hepatitis B and C
- Electrocardiography (12 lead ECG)
- Abdominal ultrasonography
- Chest X-ray

ALT = alanine transaminase; AST = aspartate transaminase; ECG = electrocardiogram; ESR = erythrocyte sedimentation rate; GGT = gamma glutamyl transaminase.

Blood tests

Blood tests on 10% random sample – As of 1 July 1999, 2,680 Gulf veterans had attended GVMAP. A 10% sample (268) of biochemical, haematological and virological/microbiological tests were chosen at random and analysed. The analysis concentrated on serum protein electrophoresis (SPE) which replaced measurement of immunoglobulins in 1997, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and antibodies to hepatitis A, B, C, cytomegalovirus (CMV) and Epstein-Barr virus (EBV). Antibodies to enterovirus, sandfly fever and serology/microbiology, ie brucella, Lyme disease and coxiella, were also done. These particular tests were chosen as clinically it seemed unnecessary to do them on a routine basis. This analysis was carried out as a result of a review of GVMAP practices¹⁶ and formed the basis of an audit carried out by the Royal College of Pathologists who considered a 10% sample satisfactory.

Blood tests on well (asymptomatic) and unwell (PTSD) sample – As a result of the audit, a further analysis was carried out. On 1 September 2002, 3,132 Gulf veterans had attended GVMAP. From these, two distinct groups were identified for analysis of blood test results. One group consisted of 310 completely well (asymptomatic) Gulf veterans and acted as controls. The other group consisted of 276 unwell Gulf veterans who had a confirmed diagnosis of PTSD. This group was selected because PTSD was the most frequent diagnosis amongst the unwell.^{9,10} None of these veterans had organic disease that could have biased the results. This group was specifically analysed because of reports suggesting low serum cortisol concentrations in such patients.^{17,18} The results of the routine serum biochemical and haematological tests were analysed and compared.

Neurological investigations

In the first 1,000 veterans who attended GVMAP between October 1993 and August 1996, there were 10 Gulf veterans who claimed excessive organophosphate exposure and 37 who presented with possible neurological symptoms, eg tingling paraesthesiae, muscle twitches or muscle weakness. These veterans

Table 2. Routine tests undertaken at GVMAP since November 2000.

- Urine analysis: proteinuria, glucosuria, haematuria
- Full blood count (not ESR)
- Blood chemistry: urea, creatinine, electrolytes, liver function (AST/ALT, GGT), thyroid function, alkaline phosphatase, T4 TSH, serum calcium and phosphate, serum creatinine, C-reactive protein and glucose
- Serology tests: hepatitis B and C, borrelia titre
- 12 lead ECG
- Abdominal ultrasonography

ALT = alanine transaminase; AST = aspartate transaminase; ECG = electrocardiogram; ESR = erythrocyte sedimentation rate; GGT = gamma glutamyl transaminase; TSH = thyroid-stimulating hormone.

were referred to the Institute of Neurology, Queen Square or the Neurology Department at University College Hospital. They underwent magnetic resonance imaging (MRI) or computed tomography (CT) brain scans, nerve conduction and electromyography tests, some had electroencephalograms (EEGs), others bone scans, cervical or lumbar spine X-rays and blood tests. In some of these cases, referrals were not strictly necessary, but at this early stage it was preferable to over-investigate these veterans since little was known about Gulf War illnesses.

Ultrasound studies of abdominal viscera

A 1,000 random ultrasound studies were selected from 3,000 Gulf veterans.¹⁰ They were analysed for any abnormalities. This study was undertaken as claims had been made by some veterans' groups that there was an increased incidence of liver and renal scarring.¹⁵

ECGs

An ECG is a routine investigation for all veterans attending GVMAP: 3,000 have been analysed.

Urinary uranium tests

There has been much media speculation about the health effects of depleted uranium exposure. We requested urinary uranium measurements if there were compelling reasons. Only two such assays were done.

Results

All veterans were seen at GVMAP by consultant physicians. Clinical findings have been reported.^{6,9,10} Importantly, 75% of all veterans attending were deemed well.¹⁰ Of the 25% who were unwell, 81% had a major or clearly significant psychiatric disorder contributing to their ill health. The remaining 19% had organic disease only. No unusual patterns of disease or unusual diseases were diagnosed.

Laboratory reference ranges are established as the mean

±2 SD of a 'normal' population. This means that 95.5% of the population falls within the reference range and 4.5% of normals fall outside. In addition, every result has an inherent error which for the analytes in this study falls between 3 and 8%. Therefore, where a laboratory result falls just outside the reference range and other parameters are normal and the subject appears healthy, such results are regarded as ONCS.

Blood test results for 10% random sample

The majority of the test results were normal (Table 3). Only two SPE results were found to be abnormal, veterans with common immunodeficiency. Only three veterans had an abnormal ESR, which reflected renal calculi in one veteran, a neuroendocrine tumour with metastases in another, and one with glomerulosclerosis. Three veterans had a raised CRP found in parallel with a raised ESR and were accounted for by known disease (*vide supra*).

The virology/microbiology investigations were all normal. Some of these were positive for antibodies to hepatitis A and B (as a result of vaccination), CMV and EBV, as would be expected in the normal population. There were no abnormal findings with respect to antibodies for enterovirus, sandfly fever, brucella, borrelia and coxiella.

On the advice of expert opinion from the Royal College of Pathologists based on this analysis,¹⁹ the following tests were withdrawn in November 2000: SPE, ESR, EBV, CMV, coxiella, borrelia and amoebic indirect fluorescent antibody.

Blood test results for well (asymptomatic) and unwell (PTSD) groups

The majority of the biochemical test results were normal (Table 4). All results for serum creatinine, sodium, potassium, albumin, calcium and phosphate, were normal in both groups.

The only significant differences found between the two groups were with respect to alanine transaminase (ALT)/ aspartate transaminase (AST) and gamma glutamyl transaminase (GGT). More were abnormal in the unwell with PTSD veterans. For ALT/AST, the odds ratio of obtaining an abnormal result was 2.37 with an associated 95% confidence interval of 1.13–4.99. For GGT, the odds ratio was 3 with a 95% confidence interval of 1.57–5.85. These differences were as expected since alcohol abuse is often associated with PTSD and all abnormal results were alcohol related except for two due to steatosis.

The one raised alkaline phosphatase result was alcohol related. The two abnormal results for thyroid-stimulating hormone (TSH) was due to suspected hypothyroidism.

All results for haemoglobin (Hb) and platelets were normal (Table 4). One white blood cell (WBC) count was abnormal but this veteran was lost to follow-up. An abnormal mean corpuscular volume (MCV) result in the well group was due to an iron deficiency. Two of the abnormal MCV results in the unwell group were due to alcohol abuse, one to medication and one to iron deficiency anaemia. There were no significant differences between the two groups.

Table 3. Blood test results for 10% random sample.

	Total	Normal**		Abnormal	
		within range	out of range but ONCS	%	%
	268*				
SPE	255	251	2 (99)	2	(1)
ESR	261	224	34 (99)	3	(1)
CRP	252	243	6 (99)	3	(1)

*Test results were not available for every veteran.
 **99% of all normal results including those within the normal range and those outside but ONCS were within 3 SDs of the mean.
 (O) means less than 0.5%.
 CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; ONCS = of no clinical significance; SPE = serum protein electrophoresis.

Results of neurological investigations

Of the 10 with alleged organophosphate exposure, four failed to attend their appointment for further neurological investigations, one had already diagnosed multiple sclerosis, one had mixed peripheral neuropathy from alcohol abuse, and four had no evidence of peripheral neuropathy.

Of the 37 with neurological symptoms, four failed to attend their neurological appointment, 26 had no evidence of any neurological disorder of which two had chronic fatigue syndrome, two had already diagnosed multiple sclerosis, one had mixed motor-sensory neuropathy, two had benign essential tremors and two had carpal tunnel syndrome.

Analysis of ultrasound studies

Eighty-five per cent of this group had normal results (Table 5). The most common abnormal liver finding was steatosis/fatty infiltration, predominantly related to obesity and/or alcohol abuse. The most common abnormal renal finding was of simple cysts.

Regarding miscellaneous findings, we found: three congenitally absent left kidneys, one left ovary cyst, one enlarged lymph

node, one transplant kidney, one chronic glomerulonephritis, one chronic pancreatitis and one gall bladder duplication.

Abnormal findings were related to known established clinical diagnoses in all but three cases. Two of these unexpected cases were hypernephromas found purely by chance in asymptomatic veterans. The other unexpected case was that of renal scarring found in a fit male with a normal serum creatinine, blood pressure and urinalysis.

Results of ECGs

ECG reports were normal or had changes consistent with known clinical diagnoses, eg ischaemic heart disease and atrial fibrillation, except for five cases. These five cases displayed unexplained Q waves in lead III. They were found in non-smoking veterans who had no family history of coronary artery disease and had normal serum cholesterol concentrations. On further investigation, which included treadmill tests, cardiac thallium scans and coronary arteriograms, all had normal cardiac structure and function. None of these ECGs would have been carried out in normal clinical practice.

Table 4. Blood test results for well (asymptomatic) and unwell (PTSD) groups.

	Well group				Unwell group				
	Total	Normal		Abnormal	Total	Normal			Abnormal
		within range	out of range but ONCS			%	%	within range	
	310*				276 ¹				
Biochemistry									
TSH	307	302	3 (99)	2 (1)	264	258	6 (100)	–	
Creatinine	308	270	38 (100)	–	274	247	27 (100)	–	
Sodium	308	293	15 (100)	–	272	260	12 (100)	–	
Potassium	308	303	5 (100)	–	273	269	4 (100)	–	
Alkaline phosphatase	309	299	10 (100)	–	273	262	10 (100)	1 (0)	
Albumin	309	278	31 (100)	–	275	249	26 (100)	–	
ALT/AST	309	271	28 (97)	10 (3)	273	234	15 (91)	24 (9)	
GGT	281	257	11 (95)	13 (5)	226	180	14 (86)	32 (14)	
Calcium	306	302	4 (100)	–	259	254	5 (100)	–	
Phosphate	295	291	4 (100)	–	254	238	16 (100)	–	
Haematology									
WBC	306	292	13 (100)	1 (0)	266	246	20 (100)	–	
Hb	307	299	8 (100)	–	266	259	7 (100)	–	
MCV	307	304	2 (100)	1 (0)	266	251	11 (98)	4 (2)	
Platelets	306	292	14 (100)	–	266	259	7 (100)	–	

* Test results were not available for every veteran.

– means none.

(0) means less than 0.5%.

ALT = alanine transaminase; AST = aspartate transaminase; ECG = electrocardiogram; ESR = erythrocyte sedimentation rate; GGT = gamma glutamyl transaminase; Hb = haemoglobin; MCV = mean corpuscular volume; ONCS = of no clinical significance; PTSD = post-traumatic stress disorder; TSH = thyroid-stimulating hormone; WBC = white blood count.

Results of urinary uranium tests

Urinary uranium was measured in two veterans and both found to be within the normal range.

Discussion

The GVMAP was set up as an assessment programme and as a quasi screening programme. Many investigations that were undertaken initially were not clinically indicated. Over the years, and on advice given, we removed routine chest X-ray, SPE, ESR, creatine kinase and some virological studies from our protocols. Apart from the chest X-ray, decisions were based on the 10% analysis of test results detailed in this paper and on advice from the Royal College of Pathologists.¹⁹ A further review of our investigation protocols by the same body has supported our current approach.²⁰

Since 75% of all veterans attending GVMAP were well, we decided to compare the biochemical and haematological results of well veterans with unwell veterans with PTSD. We not only

looked for abnormal results, but for any trends towards upper or lower limits within the normal range. We were particularly interested in serum electrolyte data to establish whether there were trends in serum sodium (downwards) and potassium (upwards) concentrations because of reports suggesting there might be a degree of hypoadrenocortical function.^{17,18,21} No abnormal trends were found. Serum cortisol concentrations were never measured.

Although early in the programme we undertook a number of investigations of the immune system function, all were found to be normal. Immunological responses (*in vitro*) are not abnormal in symptomatic Gulf War veterans.²²

When the first 1,000 veterans attended GVMAP, a number complained of non-specific neurological symptoms. They were referred to specialist neurological centres. Detailed investigations were unrewarding. One comprehensive study reported that Gulf War related neuromuscular symptoms are not associated with specific impairments of peripheral nerves, neuromuscular junctions or skeletal muscles.²³

Claims by veterans' activist groups of an increased incidence of liver or renal scarring amongst veterans prompted a random analysis of abdominal ultrasound studies. Of the 1,000 analysed, just three had an unexpected abnormality, as previously referred to, that could not have been predicted clinically. However, there was one other case of unsuspected hypernephroma found in the non-analysed 2,000 ultrasounds. Any unexpected diagnosis found on ultrasound investigation outwith the 1,000 randomly selected would automatically appear on our database. There is no comparable study for finding hypernephromas in a totally asymptomatic civilian population. In the USA, the incidence of kidney cancer has increased 43% since 1973.²⁴ We must emphasise again that none of these ultrasound studies would have been done in normal clinical practice.

Although some veterans' organisations consider that depleted uranium has been a causal factor in subsequent ill health, this has not been borne out by clinical investigations.²⁵⁻²⁸ Nevertheless, a Depleted Uranium Oversight Board has been in place since September 2001 and they have offered urinary uranium screening facilities for those veterans who have specific concerns.²⁹

It has been our policy to only undertake relevant additional investigations on clinical grounds. Requesting unnecessary investigations may reinforce concerns about the physical nature of a problem where none may exist, although in some, the negative results of investigations may prove reassuring. Anxieties may be compounded if the patient sees a new doctor at a subsequent consultation and the tests are repeated 'just to be sure'.³⁰ When undertaking a test, a patient believes that diagnostic information is becoming available. Then, if any minor aberration of a result is found which is of no clinical significance, the patient, who has the legal right of sight of his data, may feel the result is being falsely analysed or simply set aside.

After consultation with the Royal College of Physicians (1995), a wide range of investigations was undertaken, but this should now be tempered with the fact that if symptoms are so

Table 5. Abdominal ultrasound results.

		%
Total	1,000	
Normal	849	(85)
Abnormal	151	(15)
Fatty livers	78	(8)
Obesity and/or alcohol abuse	47	(5)
Haemangioma	1	(0)
Renal tract	35	(4)
Benign prostatic hypertrophy	1	(0)
Cysts	17	(2)
Duplex	4	(0)
Renal haemangioma	1	(0)
Stone	3	(0)
Scar	1	(0)
Calculi	3	(0)
Hypernephroma	2	(0)
Interstitial nephritis	1	(0)
Reflux nephropathy	1	(0)
Prostatitis	1	(0)
Pyelonephritis	1	(0)
Gall bladder disease	22	(2)
Polyps	11	(1)
Cholecystitis	2	(0)
Cholelithiasis	9	(1)
Liver and spleen abnormalities	22	(2)
Liver haemangioma	4	(0)
Liver cysts	2	(0)
Hepatomegaly	5	(1)
Splenomegaly – lymphoma	1	(0)
Splenomegaly	9	(1)
Miscellaneous	9	(1)

Some veterans have more than one abnormality.
(0) means less than 0.5%

vague, often long after any potential exposure, then a more rational approach should be adopted. As Wessely stated, 'Illnesses identical to the complaints reported by Gulf veterans are found in civilians who have never served in the Armed Forces, let alone taken part in the Gulf War'.⁴ Indeed, rather than extending the range of investigations on veterans who have so many vague symptoms similar to those seen (SSIDC) in the general public, a more appropriate 'bio-psycho-social model may provide a better solution'.³¹

Furthermore, is it appropriate that veterans be subjected to more investigations than a civilian population? Since 20%³² of the civilian population complain of the same symptoms as veterans, is this justified? Are we helping them by doing these investigations unless they are clinically indicated? A screening programme implies that there is a treatment for the patient with an abnormal test result. Thus we have never routinely tested for depleted uranium because there was never a clinical indication for so doing. Even where established cancer screening protocols are practised, this can lead to serious debate as to their value, eg prostate cancer screening,³³ and mammography.³⁴ It is important not to over-medicalise Gulf War veterans' health issues.³⁵⁻³⁷

Finally, it is difficult in financial terms to justify a routine ultrasound of abdomen (£52), ECG (£25), full FBC (£2), full biochemistry (£27) and virological tests (£49) at a cost of £157 per veteran for little or no clinical benefit, and with the potential to cause distress.

Conclusion

This audit has shown that investigations both in the laboratory and with imaging facilities of Gulf veterans, in response to various pressures rather than according to evidence-based medicine, have proved clinically unhelpful and costly. Nevertheless, we are aware from anonymised, aggregated responses to patient satisfaction questionnaires that 97% of veterans attending GVMAP are satisfied with their assessment. Such monies might be better spent improving psychiatric services for the management of post-traumatic stress disorder following conflict.^{38,39} Were another new military-related assessment unit to be set up, we recommend that investigations be restricted to those clinically indicated.

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