RAC SPEECH by Julian Pope 28.09.2015

I would like to thank the American Gulf War research and Advisory committee for this opportunity to assist you all, and the United States veterans who have invited me to speak up for their cause, here today.

We have a good idea of around 30% of all Gulf War Veterans UK and USA have what we are calling Gulf War Illness.

A Doctor recently said "If 30% of Congress got sick, or 30% of Manhattan got sick, there would have been an outcry,"

My history and why I am here.

My name is Julian Pope and I was a Reconnaissance tank Gunner during the 1st gulf War, serving as advance units with the 14/20th Kings Hussars as part of 4th Armoured Brigade.

I saw front line service throughout my time there.

Before and during the Gulf posting I was ordered to have numerous Vaccinations including anthrax (boosted with the Whooping cough Pertussis), Plague, Botulism and many many more. Vaccinations were given, One time at least, on a conveyor belt kind of system with many vaccinations given one after the other, to many many veterans, and at least once possibly 2 or 3 times whilst in the desert, during the heat of the day and during arduous battle training conditions.

We were also ordered to take the Nerve Agent Pre Treatment Set or NAPS tablets every 8 hours whilst over there.

I believe the vaccinations and pills damaged the central nervous system and specifically pituitary gland, the endocrine and hormonal system function, the Auto immune system functions, the neuropathic functions and other related system failures, inducing chronic pain and chronic fatigue as well as other life consuming conditions.

As well as the vaccinations and Nerve Pills We were exposed to various degrees of chemical warfare agents due to repeated air bombing of chemical weapons dumps, as was shown with the 14,000 or so separate and repeated chemical alarms that went off over there, which we were told to ignore as they were, all 14,000 or so, said to be 'false Alarms'. The various chemical weapons dump destructions, such as Khamisayah were never really explained to anyone at the time although the repeated large dust clouds that 'turned day into night' were seen by many on the ground and now are believed to contain various contaminating Chemical warfare agents.

Depleted Uranium, from our own ammunitions, also littered the battlefield and was a massive threat to all of us, which was underplayed, if mentioned at all.

That's my history and why I am here.

I suffer with all the symptoms that you can imagine and all that are often mentioned as regards Gulf War Veterans. I appear to function very well due to my ability to pretend that my cognitive and concentration is better than it actually is and I also have an extremely

high tolerance to pain, having suffered excruciating pain for many many years with little or no treatment up until the last 4 or so years.

I have been ignored over the years after many doctors dismissed my pain as being 'inexplicable' and psychological in nature, and especially after one high ranking professor in the UK told the UK parliament and our Health Service that our illnesses were purely PTSD related.

In around 2003 A veteran in Hull UK (Shaun Rusling) underwent treatment with an Endocrinologist unit under the leadership of Professor of Endocrinology Stephen Atkin. After incredible results a research study was performed in 2007, on 19 Ill gulf war veterans, and a paper was peer reviewed and published relating to the Gulf War Syndrome or gulf war Illnesses. The paper discussed incredibly rare Hypopituitarism, Hypogonadism, hypothyroidism, with complicating issues and symptoms such as chronic pain and chronic fatigue.

Imortant Pituitary conditions that need explaining

Pituitary disorders are considered rare, sometimes appearing naturally and sometimes appearing in a small percentage of patients with traumatic brain injury. It is estimated that there are between 50,000 and 70,000 pituitary patients in the United Kingdom, which equates to 0.08% - 0.11% of the general 64,000,000 population inclusive of brain injury or any other patient or non-patient group.

We, as a group of UK veterans, think, as of latest numbers, that 30 out of 33 Ill gulf War Veterans tested, using the Gold Standard Insulin Stress Test (or what you Americans would call the insulin tolerance test.) have shown to be positive for having COMPLEX pituitary disorders.
There are more veterans in the UK testing pipeline that have been done but we don't want to randomly pluck the numbers out of the air. Further figures, without helpful and massively overdue assisted research will prove slow and difficult, as both the UK and American Government both know

In other words, to find 1 person from within a population of people in which some might have had a traumatic brain injury, or ex-military service people, with ANY of these problems you would have to test around 1,066 people with the GSIST.

So, in order to find 30 people with these diagnoses you would have to test 31,980.

ONLY 33 have been tested to find 30 people with these problems in the UK.

Those Ill Gulf War Veterans that have been proven positive have a rarer more complex Hypophysitis hypopituitary diagnosis so the numbers likely to have to be tested to find this amount of people with these complex issues would be MUCH MUCH higher.

Since around 1996 I, and many others, have fought for Gulf War Illness sufferers to be recognised in the UK, and the US, and for reasons above, I have been ridiculed and ignored by my own doctors and various entities on the internet. I have had incredibly tough and dark days as have many others but that's not why I'm here.

During the last 4 years especially, I have watched whilst many of my fellow veterans in the UK and USA have been ridiculed and humiliated by doctors who should know better than to treat such a vulnerable group of heroes so disgracefully.
I have also watched it happen here, in the USA, via the internet, in what you call the Government run VA. Doctors telling patients that they should 'Stop researching stuff all the time… stop listening to other veterans…..

Stop asking for stupid tests that they have never heard of… stop researching and thinking too much about it… see a psychiatrist….. Stop talking to friends who are doctors and nurses… stop bothering them with this all the time!'
I have been appalled at my own treatment and further appalled by the treatment of men and women who have done nothing other than try to serve their country

I have watched as repeated studies have taken place regarding mitochondrial attributes etc and I have repeatedly sent ALL the information to anybody and everybody that would listen. Universities, research study groups, doctors. I have watched unusual study participant requests come and go, one after another, time after time 10, 20, 30 or so a year? I lose count. I have tried to repeatedly contact facebook entities that appear to be in charge or have some sway but little has happened as regards the fact that in the UK 33 Ill gulf veterans have been tested and 30 of those have been found to have this incredibly rare physical set of conditions that just so happens to fit the symptoms of Gulf war Syndrome Exactly.

I must emphasise - In order to find 30 people, within a general population, including veterans, you would have to have tested, according to the highest official body of UK endocrinologists, 31,980 people.
And yet it only took 33 ill Gulf war Veterans to be tested, not all of which, were deployed.

I implore you to undertake a research study of ill Gulf War Veterans by fully qualified specialist endocrinology departments.
I beg that you test around 30 deployed veterans and 30 non deployed veterans using the American version of our Gold standard Insulin Stress test, called the Insulin Tolerance test (not glycogen test or any other less sensitive test).

The test MUST include all VACCINATED veterans of a mixture between non deployed and deployed and preferably be chosen by a veteran led body to insure transparency of conduct and to build trust between the VA and the veterans which is so sorely lacking now.

I also finally request that you work alongside a UK / Allied veteran led group regarding all discussion, treatment and findings etc at every level.

In the words of the veteran first studied and found to have these ailments, Shaun Rusling;
'We have damage to the Neuro-endocrine system, dysfunctional hypothalamus, Pituitary failure caused by NAPS (PB) and an erroneous cocktail of live and dead vaccines boosted by experimental adjuvants crossing the blood brain barrier, leaving an opportunist bacterial infection (autoimmune) which causes a cascade effect when we are stressed. Our illness is firstly related to this aspect all other exposures are secondary to this, and compounded by secondary exposures.

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SAT-0735:
Pituitary Dysfunction in Gulf War Syndrome Patients - a Case Series

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- ABSTRACT

Abstract:

Introduction

Gulf war syndrome (GWS) is described as a cluster of medically unexplained chronic symptoms of fatigue, headache, musculoskeletal pain, skin disorders, sleep disturbances and neuro-cognitive disorders in veterans of the first Gulf War. Studies have shown subtle changes in the hypothalamic-pituitary-adrenal axis in the Gulf war veterans with GWS. We present a case series of patients with diagnosis of GWS who underwent dynamic pituitary testing.

Methods

We have retrospectively analysed the seven gulf war veterans who presented to us in the last 18 months with diagnosis of GWS and ongoing fatigue. All of them underwent baseline pituitary profile, 9 am testosterone, sex hormone binding globulin and thyroid function tests. This was followed by pituitary dynamic testing: insulin stress test (IST) or glucagon stimulation test (if IST contraindicated), thyrotropin releasing hormone stimulating test and gonadotropin releasing hormone stimulation test.

Results

All patients were male, with a mean age of 46.28 years. Two of the seven patients (28.6%) had normal hypothalamo-pituitary function. Rest of the 5 patients (71.4%) had various pituitary hormonal deficiencies of which all patients had hypothalmic-pituitary-adrenal axis dysfunction needing steroid replacement. Four patients had suboptimal growth hormone response and low adult growth hormone deficiency quality of life (AGHDA QoL) questionnaire response needing growth hormone replacement. One patient had hypothalmic-pituitary-gondal dysfunction needing testosterone replacement. All patients had normal MRI scan of pituitary. All patients who needed replacement had variable improvement in their symptoms after 6 months of replacement.

Conclusion

Hypothalamic-pituitary dysfunction is associated with Gulf War Syndrome. Pituitary hormone replacement therapy in this cohort of patients with hormonal dysfunction could improve some of their symptoms and quality of life.

Nothing to Disclose: NPP, SLA, TS

were found in 33·3% of the AQP4 CNS AI patients (in 4/12 for TG and 3/9 for TPO, respectively), in MS patients this was only the case for TG in 22·2% (2/9) and not observed for TPO antibodies.

This study indicates a distinct pattern of the thyroid antibodies TG and TPO in AQP4 CNS AI and MS with regard to seroprevalence and immunoreactivity. In paediatric CNS AQP4 AI autoantibodies were detected in up to 76%, with a 13% rate of TPO antibodies.[5] The prevalence for TPO antibodies was slightly higher in our mainly adult and exclusively female cohort (20·9%), and immunosuppressive therapy in AQP4 CNS AI may have even lowered the observed prevalence and titres. It needs to be considered that TPO antibodies are regularly detected in SLE and SS which are among the most frequent autoimmune disorders associated with NMO.[6] Seroprevalences of TG/TPO in the literature for MS vary, with similar frequencies in Austrian MS patients and controls and a Spanish study demonstrating an almost five time higher prevalence rate for TG antibodies in MS.[7,8] We did not observe differences in the seroprevalence between MS and control patients. However, our samples sizes were rather small, and the utilization of different assays and cut-offs need to be taken into account. Moreover, the presence of patients with other neurological disease in the control group may have obscured the prevalence in truly healthy subjects. Most interestingly, a subgroup of AQP4 patients had very high TPO antibody titres (33·3%), which was not seen in the other two cohorts. A genetic predisposition may be considered, since Caucasian AQP4 CNS AI is frequently associated with human leukocyte antigen (HLA)-DR3.[9] This haplotype was evaluated in healthy blood donors and shown to confer not only a risk for antibody positivity, but also high TPO-titres (>350 IU/ml).[10] Thus, whether the presence of thyroid antibodies in CNS AQP4 AI is an epiphenomenon, indicates asymptomatic thyroiditis or is a risk factor for developing Hashimoto's thyroiditis, or even plays a pathogenetic role in a subgroup of patients, warrants further study.

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References

1 Jarius, S. & Wildemann, B. (2010) AQP4 antibodies in neuromyelitis optica: diagnostic and pathogenetic relevance. *Nature Reviews Neurology*, **6**, 383–392.

2 Kim, W., Park, M.S., Lee, S.H. *et al.* (2010) Characteristic brain magnetic resonance imaging abnormalities in central nervous system aquaporin-4 autoimmunity. *Multiple Sclerosis*, **16**, 1229–1236.

3 Pittock, S.J., Lennon, V.A., de Seze, J. *et al.* (2008) Neuromyelitis optica and non organ-specific autoimmunity. *Archives of Neurology*, **65**, 78–83.

4 Kalluri, S.R., Illes, Z., Srivastava, R. *et al.* (2010) Quantification and functional characterization of antibodies to native aquaporin-4 in neuromyelitis optica. *Archives of Neurology*, **67**, 1201–1208.

5 McKeon, A., Lennon, V.A., Lotze, T. *et al.* (2008) CNS aquaporin-4 autoimmunity in children. *Neurology*, **71**, 93–100.

6 Weetman, A.P. (2011) Diseases associated with thyroid autoimmunity: explanations for the expanding spectrum. *Clinical Endocrinology*, **74**, 411–418.

7 Niederwieser, G., Buchinger, W., Bonelli, R.M. *et al.* (2003) Prevalence of autoimmune thyroiditis and non-immune thyroid disease in multiple sclerosis. *Journal of Neurology*, **250**, 672–675.

8 Munteis, E., Cano, J.F., Flores, J.A. *et al.* (2007) Prevalence of autoimmune thyroid disorders in a Spanish multiple sclerosis cohort. *European Journal of Neurology*, **14**, 1048–1052.

9 Zephir, H., Fajardy, I., Outteryck, O. *et al.* (2009) Is neuromyelitis optica associated with human leukocyte antigen? *Multiple Sclerosis*, **15**, 571–579.

10 Boehm, B.O., Kuhnl, P., Loliger, C. *et al.* (1993) HLA-DR3 and HLA-DR5 confer risk for autoantibody positivity against the thyroperoxidase (mic-TPO) antigen in healthy blood donors. *Clinical Investigation*, **71**, 221–225.

Pituitary hypophysitis and gulf war syndrome: a case series and hypothesis

The Gulf War Syndrome (GWS) is a well described cluster of symptoms of musculoskeletal pain, skin disorders, headache, memory loss, neurocognitive disorders and sleep disturbance among other symptoms in Veterans of the First Gulf War.[1] Post war Surveys estimated that almost 17% and 18% of deployed British and US troops respectively had symptoms compatible with the syndrome. Studies have shown subtle changes in the hypothalamopituitary–adrenal (HPA) axis in Gulf War Veterans (GWV) with the GWS. However, there are no reports on dynamic pituitary testing in GWV.[2]

During the investigation of these patients the hypothalamic–pituitary axis of 11 sequential GWV males with a known diagnosis of GWS was undertaken. The prior diagnosis of GWS was made either by the General Practitioner or other secondary care services after multiple symptoms complaints in the presence of normal routine general investigations in GWVs. Ethical approval was not sought since the investigations were part of routine clinical practice. All subjects underwent baseline pituitary, 9:00 AM testosterone, sex hormone binding globulin (SHBG) and thyroid function tests followed by pituitary dynamic tests; insulin tolerance test (ITT)/glucagon stimulation test (if ITT is contraindicated), thyrotropin releasing hormone (TRH) stimulating test and gonadotropin releasing hormone (GnRH) stimulation test as per standard protocols.[3–5] Those with one or more abnormality of the pituitary dynamic tests also underwent MRI of their pituitary gland. A health questionnaire specific to GWV was used to assess their health at baseline and again after treatment if hormonal replacement was indicated and prescribed.[6] The questionnaire used the visual

analogue scale (10 cm in length), ranging from 'not at all' to 'very seriously', how much they had been troubled by 95 symptoms. The average of scores in each questionnaire for each individual before and after replacement were analysed using a paired t test.

The mean and standard deviation of the weight and body mass index were 92 ± 20 kg and 27·6 ± 5 kg/m^2, respectively. In our series, all but two (subject 6 and 8) of the 11 GWV had one or more abnormal component of the combined pituitary test, seen in Table 1. Treatment with hormonal replacement based on low baseline hormones as well as abnormal dynamic tests was indicated in six (54·5%) subjects of whom one did not tolerate the indicated therapy. Subject 1 had low baseline testosterone, abnormal growth hormone (GH) and cortisol response to ITT as well as abnormal GnRH test but he reacted adversely to all forms of hormonal replacement therapy and declined further treatment. Subject 7, 10 and 11 had abnormal GH response to ITT combined with abnormal GnRH response and low baseline testosterone and gonadotropins. Consequently they received growth hormone and testosterone replacement. Subject 3 had a flat cortisol and GH response to glucagon stimulation test and he received corticosteroid replacement. Subject 4 had low free thyroxine and low baseline testosterone and gonadotropins in addition to suboptimal ITT, TRH and GnRH responses and therefore received replacement with hydrocortisone, thyroxine and testosterone.

Table 1. Results of the pituitary investigations of 11 Gulf War Veterans with Gulf War Syndrome

Patient*	Max GH (mIU/l)	Max cortisol (nmol/l)	GnRH test	TRH test
1†	3·9	440	Abn‡	N§
2	24·7	920	Abn	N
3†¶	0·3	60	N**	N
4	20·1	362	Abn	Abn††
5	33·6	687	Abn	N
6	13·2	662	N	N
7‡‡	7·4	634	Abn	N
8	18·6	652	N	N
9	54·2	579	Abn	N
10	5·9	612	Abn	N
11	6·0	754	Abn	N

N, normal; Abn, abnormal.
A normal GH response to the insulin tolerance test (ITT) and glucagon stimulation tests is ≥10 mIU/l (GH unit in mIU/l is equal to three folds the old unit in micrograms per litre). Normal ACTH reserve was defined as a maximal cortisol after adequate hypoglycaemia of ≥500 nmol/l for the ITT and a post glucagon stimulation cortisol level of ≥500 nmol/l.
*Patients are numbered in sequential order, 1 = patient 1, 2 = patient 2 and so on.
†The patients with empty sella finding on the MRI.
‡Lack of normal response of LH.
§TSH at 20 min of more than 5·5 mU/l but <20 mU/l.
¶The subject who had glucagon stimulation test instead of ITT.
**Peak LH 20–30 min after injection which exceeds the upper end of the normal range.
††Inadequate, absent, delayed or a prolonged TSH response.
‡‡The patient with bulky pituitary.

There were three GWV (subjects 2, 5 and 9) with an isolated abnormality of the GnRH test but normal baseline testosterones and therefore treatment was not indicated.

In total, a suboptimal GnRH response was evident in eight (72·7%), while three (27·2%) had suboptimal cortisol responses, two to ITT and one to glucagon stimulation test (subject 3). GH deficiency was seen in five (45·4%); four of which had normal BMI (M = 23 kg/m^2, SD = 1) and only one was obese, BMI of 33 kg/m^2. Abnormal response to TRH was recorded in one GWV. Two of the GWV had empty sella on MRI of the pituitary and another had a bulky pituitary gland on MRI while the rest had normal pituitary.

Only subject 9 did not return a completed questionnaire. The mean and SD of the overall baseline scores were 5·9 (maximum is 10) and 2·3 respectively. For those who received hormonal replacement therapy (n = 5), there was a significant improvement in the mean scores after treatment (M = 4·9, SD = 1·4) compared to the baseline (M = 6·44, SD = 1·3, $P < 0·05$).

To our knowledge this is the first clinical report on the association between anterior hypopituitarism and GWS. Although the cause of the GWS remains unidentified, recent studies have hypothesized that permanent psychogenic stress coupled with high antigen loading leading to gradual depletion of HPA axis, which is manifested by the reduction of stress-induced cortisol response.[2] The explanation for the high frequency of abnormal anterior pituitary function in our series could be offered by the above hypothesis of chronic stress, although our findings were not exclusive to the HPA axis, perhaps indicating a more diffuse effect on the anterior pituitary than originally hypothesized. Furthermore, in the five subjects who tolerated the hormonal replacement therapy, the administered health questionnaire showed a significant improvement in the scores after replacement, although this improvement was not substantial which indicates that there could be other causes for the multitude of symptoms encountered by GWV. It is also plausible that this improvement in wellbeing could regress to the mean with time. In conclusion, our case series shows unusually high clustering of abnormal pituitary dynamic tests in GWV with the GWS possibly related to immunogenic hypophysitis. This may help explain some of the complex and multiple symptoms experienced by those afflicted by GWS.

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References

1 Ismail, K. (2001) A review of the evidence for a "Gulf War syndrome". *Occupational and Environmental Medicine*, **58**, 754–760.

2 Golier, J.A., Schmeidler, J. & Yehuda, R. (2009) Pituitary response to metyrapone in Gulf War veterans: relationship to deployment, PTSD and unexplained health symptoms. *Psychoneuroendocrinology*, **34**, 1338–1345.
3 Besser, G.M., McNeilly, A.S., Anderson, D.C. *et al.* (1972) Hormonal responses to synthetic luteinizing hormone and follicle stimulating hormone-releasing hormone in man. *British Medical Journal*, **3**, 267–271.
4 Cain, J.P., Williams, G.H. & Dluhy, R.G. (1972) Glucagon-initiated human growth hormone release: a comparative study. *Canadian Medical Association Journal*, **107**, 617–622.
5 Landon, J., Greenwood, F.C., Stamp, T.C. *et al.* (1966) The plasma sugar, free fatty acid, cortisol, and growth hormone response to insulin, and the comparison of this procedure with other tests of pituitary and adrenal function. II. In patients with hypothalamic or pituitary dysfunction or anorexia nervosa. *Journal of Clinical Investigation*, **45**, 437–449.
6 Cherry, N., Creed, F., Silman, A. *et al.* (2001) Health and exposures of United Kingdom Gulf war veterans. Part I: the pattern and extent of ill health. *Occupational and Environmental Medicine*, **58**, 291–298.

Evaluation of MEN1 risk in individuals bearing R171Q. R171Q – single nucleotide polymorphism (SNP) or not SNP – that is the question

The assumption that the R171Q-variant of the *MEN1*-gene represents a low penetrance point mutation for multiple endocrine neoplasia type 1 (MEN1) rather than a polymorphism is based on the observation that, in the absence of other disease causing *MEN1*-mutations, the R171Q-variant was found in two unrelated pedigrees with a MEN1-related state, but not in 50 control subjects.[1]

The uncertainty whether R171Q represents a single nucleotide polymorphism (SNP) or a mutation in one patient with a pancreatic tumour and in relatives of a patient clinically diagnosed with MEN1 (not available for further analyses) encouraged us to undertake the following study: R171Q was analyzed in 513 individuals including patients with suspected MEN1 (n = 100) *vs* control populations including MEN2 (n = 128), insulin dependent diabetes mellitus (IDDM, n = 144) and congenital adrenal hyperplasia (CAH, n = 141) using restriction fragment length polymorphism (RFLP)-analysis (PCR followed by NciI-digestion), TaqMan-SNP-Genotyping (rs607969), sequencing of *MEN1*-exons 2–10 and multiplex ligation dependent probe amplification (MLPA)-analysis (AIP-MEN1 Salsa MLPA kit; MRC-Holland, Amsterdam, Netherlands). This represents the largest number of MEN1-unrelated alleles so far analysed for R171Q at the germline level. Moreover, R171Q was analysed in 50 MEN1-related and 50 unrelated tumours.

In contrast with DeCarlo's observation,[1] our study clearly shows that the R171Q-allele-frequency was similar in patients with suspected MEN1 (1·5%) and in the control populations (1·35%), being highest in IDDM (1·75%) and lowest in CAH patients (0·7%).

Concerning tumour tissue, R171Q-heterozygosity was found in one struma, whereas both the R171Q-aberration and loss of heterozygosity (LOH) were detected in our patient's pancreatic endocrine tumour and in one phaeochromocytoma, resulting in a R171Q-allele frequency of 1·5%. In both tumours LOH comprised one MEN1-gene and seven reference genes at 11q13, but not the control genes (not located on chromosome 11).

Whereas the pancreatic tumour had lost the 171Q-allele and the phaeochromocytoma the wild type-allele 171R, a major role of R171Q in the development of multiple endocrine tumours due to a MEN1-syndrome appears unlikely – otherwise, according to Knudson's two hit hypothesis,[2] both tumours would have lost the wild type copy.

The observations of our study and of a previous report by Balough *et al.* [3] that the R171Q-allele frequency was inversely related to the number of MEN1-related lesions and was higher in patients with 'MEN1-related' disease than in 'MEN1-diagnosed' ones, suggest a potential role of the R171Q-aberration specifically in 'MEN1-related' disease, but not in MEN1-patients identified to carry a *MEN1* mutation.

Since R171Q occurs in different populations as well as in 100 MEN1-related and unrelated tumours in a similar frequency, we assume that R171Q has no significant role in MEN1-related tumour formation but more probably represents a polymorphism with lower relevance and penetrance than a MEN1-causing mutation.

Such differentiation between SNP and disease-causing mutations is of major importance in order to confirm clinical diagnosis, to identify phenocopies, to drive therapeutic decisions and provide optimal genetic counselling.

By its location in transcription factor (JunD, Smad3) and co-factor binding domains of the *MEN1*-gene,[4,5] R171Q could, however, influence different signal transduction cascades and so far undefined MEN1-related biological processes and clinical phenotypes.

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References

1 De Carlo, E., Pilon, C., Zatelli, M.C. *et al.* (2008) Isolated R171Q amino acid change in MEN1 gene: polymorphism or mutation? *Clinical Endocrinology*, **69**, 511.
2 Knudson, A.G. (2001) Two genetic hits (more or less) to cancer. *Nature Reviews Cancer*, **1**, 157–162.
3 Balogh, K., Hunyady, L., Patocs, A. *et al.* (2007) MEN1 gene mutations in Hungarian patients with multiple endocrine neoplasia type 1. *Clinical Endocrinology*, **67**, 727–734.
4 Agarwal, S.K., Guru, S.C., Heppner, C. *et al.* (1999) Menin interacts with the AP1 transcription factor JunD and represses JunD-activated transcription. *Cell*, **96**, 143–152.
5 Kaji, H., Canaff, L., Lebrun, J.J. *et al.* (2001) Inactivation of menin, a Smad3-interacting protein, blocks transforming growth factor type beta signaling. *Proceedings of the National Academy of Sciences of the United States of America*, **98**, 3837–3842.