Unfortunately Miss Smith, who was due to attend me for consultation on the 12th October, was unable to attend; however we used the time to discuss her case over the telephone.

History:
Essentially there is an approximately 5 year history of chronic fatigue, predominated by severe muscle weakness and weight gain. The associated features are generally sore throat, flu-like symptoms and unrefreshing sleep.

About 2 years ago she had a quite significant relapse with marked dizziness, reduced energy, pains in the muscles of the arms and legs, and headaches. At this point she was diagnosed with ME after numerous blood tests and she instigated pacing. This improved her quality of life, and she is now able to do about 20% of previous activities. If she goes beyond this, she becomes significantly worse. Even at this level she can sometimes have episodes of worsening.

Past Medical History:
She has had recurrent and frequent tonsillitis and on 2 occasions requiring admission to hospital and intravenous antibiotics. She also has multiple abscesses also requiring admission to hospital previously. She has had persistent weight gain for the last 5 years, and this is despite restricting calories below 2000 daily. She has no known drug allergies.

Family History:
There is a strong family history of phaeochromocytoma; indeed everyone in her extended maternal family has suffered this condition apart from Tracey. There is also a history of emphysema at a young age, and arthritis.

Pre-Morbid State:
She was an active wife and mother. She has had 12 long-haul flights in the space of 6 years. She did a lot of outdoor activities, although there was no severe exposure to insects or other vector-borne illnesses.

Variation of Symptoms:
She usually varies from day to day, or from week to week. She does not really vary throughout the day.

There is a link with her menstrual cycle in that she does feel her symptoms more acutely when she is menstruating. There is a non-offensive PV discharge, and she has had an ultrasound of the pelvis, which was reported as negative.

On Systematic Enquiry:
She has suffered from variable bowel habits for several years. She has had many courses of antibiotics for the tonsillitis.

Impression:
As I have not had an opportunity to examine her, the differential diagnosis remains wide. I would also appreciate seeing her test results.

I think Addison's disease and hypothyroidism have been excluded already. Other possibilities include dysbiosis, chronic viral infection, Strep-induced immune dysregulation and possibly the most likely, given her weight gain, fat-soluble toxin accumulation.

Plan:

1. I have requested copies of the results of her previous investigations, and if you could send these, that would be very helpful.
2. She will attend here for a full autonomic profile and to be reviewed by me.
3. I suspect that she will require the following investigations, but I will confirm this once I have examined her:

    - Haematology and biochemistry profiles with electrolytes

- DNA adducts evaluation
- Translocator protein study
- Intracellular calcium full studies
- Comprehensive viral panel
- Gastrointestinal function profile and parasitology

I will let you have the results of her investigations once these are to hand. If you have any queries regarding the above, please do not hesitate to contact me.

Impression:
Immunotoxicity.

Plan:
1. Depuration programme.
2. ?Antiviral treatment, such as Imunovir, following this.

I spoke with her and her partner on the 22nd March to discuss her results. There was a clear IgM response to HHV6. This has been linked with chronic fatigue syndrome and is likely to be responsive to either Imunovir or Valtrex. The cause for this unusual and sustained infection is likely to be toxin-related. As you may be aware, this is the MRC's prioritisation for research into chronic fatigue syndrome. I enclose a copy of their prioritisation list.

The toxin was an unusual compound, which seemed to be partly from dye products, and also from smoking. Tracey has stopped smoking and the use of any dyes, and is undergoing a nutritional detox programme. But still smokes now

I will write again after I have reviewed her in 3 months' time, all being well. Please do not hesitate to contact me if you have any queries regarding the above.

Further to my letter of the 2nd November, the results of Miss smith's investigations are now to hand (copies enclosed).

Haematology profile was normal.

Biochemistry profile showed low bicarbonate at 21 mmol/l (NR 22-29), raised cholesterol at 6.6 mmol/L (NR <5.0) and raised iron at 30.0 umol/L (NR 6.6-26.0).

Comprehensive viral panel showed the following:

IgG HSV 1+2	*High at 24.40 EU/mL*	*NR 24.40*
IgG HHV-6	*High at 65.41 EU*	*NR <51.00*
IgM HHV-6	***High at 44.31 EU***	***NR <29.00***
IgG Varicella-zoster	*High at 2.07 ISR*	*NR <0.9*
IgG Rubella/Measles	*High at 2.36 ISR*	*NR <0.9*
IgG Epstein-Barr VCA	*High at 3.15 ISR*	*NR <0.9*
IgG EB Nuclear Antigen	*High at 2.40 ISR*	*NR <0.9*

DNA adducts evaluation was normal.

Intracellular calcium studies showed high protein-bound intracellular calcium but it is magnesium responsive. Ca-actin binding that affects the cytoskeleton and lowers the normal cell-motility.

Translocator protein studies showed a moderate level of Azo-benzene, a trace of Tartrazine and high intracellular calcium with Ca-actin binding.

Gastrointestinal function profile showed slight malabsorption and low levels of healthy flora.

I will review Miss smith with the results of her investigations and will keep you informed of my further recommendations and her progress.

Further to my letter of the 30th March, the results of Miss smiths's recent investigations are now to hand (copies enclosed).

Ferritin level was within the normal range, but was lower than the optimum ferritin level for females, which is >27 ug/L.

Endocrinology profile was normal.

Further to my letter of the 20th April, the results of furhter investigations are now to hand (copies enclosed).

Toxic effects of chemicals identified by other tests showed pre-existing inhibition of metabolic activity to Azo-benzene, mild pre-existing inhibition of metabolic activity to Tartrazine, and pre-existing inhibition of metabolic activity to Naphthols (alpha & beta).

Fat cell pesticides screen showed that traces of both alpha and beta-naphthols are present.

I will review her results and will keep you informed of my further recommendations and her progress.

Particulars: A 40-year old female was referred for autonomic function test with a clinical impression of: Dysautonomia associated with chronic fatigue.
Body Mass Index: was 30.1 kg/m^2 indicating that he is overweight (Normal range, 19-25 kg/m^2).

Results

Cardiovascular reflexes: ***Resting cardiac vagal tone (CVT)*:** was 3.0 units in the linear vagal scale (LVS) which is a low resting cardiac vagal tone, (Normal range, 5-10 units in the LVS), associated with no Abnormal Spontaneous Brainstem Activation (ASBAs). There was low spontaneous baroreflex function. ***Resting heart rate:*** was 89 beats/min, which is a mild tachycardia consistent with this level of CVT. *Breathing*: there was normal breathing at the rate of 16 breaths/min. ***Deep breathing:*** CVT was 17.58 units and the maximum CVT was 25.12 units in the LVS indicating over-reaction of CVT in the brainstem during deep breathing. ***Carotid massage:*** CVT increased by 2.1 units in the LVS showing a low cardiodepressor effect (normal increase 5-20 units), blood pressure (BP) changed by -3.8 mmHg indicating a low vasodepressor effect (normal drop 10-25 mmHg). ***Baroreflex responsiveness in isometric exercise:*** was 0.49 ms/mmHg but 1.71 ms/mmHg was predicted from the patient's height, it indicates a lower than normal central gain of the baroreflex system. ***Valsalva's ratio:*** was 2.35 indicating a higher than normal Valsalva's ratio (normal range, 1.2-1.8).

***Nutritive Peripheral Circulation*:** Supine pO_2 was 64.0 (should normally be above 60 mmHg) and supine pCO_2 was 41.1 mmHg (normal range; 39-44 mmHg). There was good nutritive gaseous exchange in peripheral tissues at rest. There were also good responses of gaseous levels in peripheral tissues during deep breathing.

Orthostasis: ***Cardiac response:*** showed an abnormally low response in a 30:15 ratio test. ***BP stability:*** was poor, systolic BP varied by -56.0 mmHg, normal variation is <25 mmHg. Mean supine arterial BP was 72.8 mmHg indicating a moderate supine hypotension (the normal range of supine mean arterial BP, 80-110 mmHg). ***Orthostatic hypotension:*** Postural change in diastolic BP was 3.8 mmHg. Therefore, no postural hypotension was detected. There was inotropic fatigue on standing upright.

Sympathetic function in general: There was no test done for postganglionic damage. The BP evidence suggests a low baseline supine sympathetic tone. There was good baseline inotropic function. ***Control of resistance blood vessels in skeletal muscles during isometric exercise:*** showed muscle sympathetic failure. There was inotropic fatigue on sitting upright. ***Cardioaccelerator function in isometric exercise:*** showed a cardioaccelerator failure. There was normal inotropic response to isometric exercise. ***Blood pressure response to Valsalva's manoeuvre:*** BP change in phase IIe was -29.0 mmHg and in phase III was 32.0 mmHg showing evidence of reduced venous return. BP change in phase IIi was 70.0 mmHg indicating a markedly raised splanchnic sympathetic tone.

Interpretation: The results show evidence of muscle sympathetic failure, cardioaccelerator failure but a markedly raised splanchnic sympathetic tone in the deep target organs of the sympathetic division of the autonomic nervous system. There was evidence of reduced venous return to the heart. In the parasympathetic division, there was a low resting cardiac vagal tone. Baroreflex system had a low central gain and there was

over-reaction of the CVT in the brainstem during deep breathing. There were low cardiodepressor and vasodepressor effects of the carotid reflex. Of the non-specific tests, there was no postural hypotension, a high Valsalva's ratio and abnormally low response of the heart to standing upright.

Conclusion and Recommendations: This patient has both sympathetic and parasympathetic dysfunctions. Sympathetic failure was limited in the target organs in the heart and in skeletal muscles. The markedly raised sympathetic tone in the splanchnic vascular bed can be compensatory to failure elsewhere, but can also be due to increased immune activity in this patient. There was extensive central baroreflex failure associated with a moderate to severe decrease in parasympathetic tone. She however has good nutritive gaseous exchange in peripheral tissues at rest and the good response during deep breathing suggests good diffusion pathway to peripheral tissues. This patient should be investigated for general allergy, particularly to food additives. The inotropic fatigue associated with contraction of postural muscles means this patient will have exercise intolerance and will fatigue easily. She therefore requires medical support of the inotropic function of the heart through dietary supplements.