

# **Network MESH West London**



**Dr. Charles Shepherd**  
**Medical Adviser to the ME Association,**  
**Guest Speaker at Network MESH AGM**  
**Transcription - Talk and Q&A**  
**Tuesday 23 October 2012**

TONY GOLDING: Can I say a few things before we start? Welcome to everybody, especially people who are not members. For those of you who do not know, Network MESH is an independent ME support group with 125 members. We have been around for 22 years. Because we are a registered charity, we have to have an AGM, so technically this is our AGM. What we are going to do is what we normally do. We invite a speaker, as we have done today. We will have ten minutes at the end for any member who wants to stay to do the formal stuff that we have to do, because we are a charity.

For many people I do not think I really need to introduce Dr Shepherd. That is because anybody who has had ME for any length of time will know him, as he has been fighter for people with ME for many, many years now. He is the Honorary Medical Adviser of the ME Association (MEA). We thought he would talk for about 45 minutes and then we will break for coffee. We will then have Q&As for maybe half an hour.

Rob is going to video this to put it on the group website and Carolyn, whose sister has ME, is actually going to write it down verbatim, so we are going to get a proper transcript of the whole thing. We will also put the slides on the website as well.

I am very conscious, as ever, that there are lots of people with ME who are just not well enough to come to something like this. People often ring me up and say, "I'm going to come," but on the day it is too much for them.

CHARLES SHEPHERD: First of all, I was going to start by explaining a little about who I am and where I am coming from in all this. First of all, I live in Gloucestershire and that is where my home is. I do have a picture, which you will see shortly, of what we call the Chalford Hill donkey, which is our claim to fame where I live in Chalford Hill. We live on the top on a hillside and we still have a little donkey delivery that zigzags up the donkey tracks of Chalford Hill delivering the bread on a Saturday morning. Anyway, that is our Chalford Hill donkey!

The next slide I was going to show you was the Royal Free Disease back in 1955. I was going to put it up because I trained at the Middlesex Hospital in central London back in the early Seventies. Unfortunately, if you know central London, you will know Mortimer Street and you may have seen that the Middlesex Hospital is now just a pile of rubble. But that is where I did my medical training.

While I was at the Middlesex in the early Seventies, when I was doing the psychiatric bit of my medicine, I was on firm with two psychiatrists called Doctors Macavity and Beard. It was at that time, in the 1970s, that

Macavity and Beard published a paper in the *British Medical Journal* on what was called The Royal Free Outbreak. This was where Myalgic Encephalomyelitis got its name, because all these people in the mid-Fifties were going down in North West London with this mysterious – what people thought was perhaps a polio-like – illness, being admitted to hospital and a considerable number of hospital staff also went down with this illness (292 doctors and nurses). It resulted in the Royal Free being closed for a short period of time. My colleague – because I knew Melvin Ramsey quite well over the years – who was the consultant in infectious diseases at the Royal Free Hospital saw the patients, diagnosed these cases and they were written up in *The Lancet* the following year. There was an accompanying editorial in *The Lancet*, written by Sir Donald Aitchinson, who was a former Chief Medical Officer of Health. That is where the term myalgic encephalomyelitis came into being. It was introduced in *The Lancet* editorial, following the Royal Free Hospital outbreak.

The psychiatrists from the Middlesex Hospital went back and reviewed these cases, published this paper in the *BMJ* in the mid-Seventies, when I was at medical school, and concluded that Royal Free Disease (myalgic encephalomyelitis) was all hysterical nonsense. So doctors like myself – and doctors I think for many years to come – left medical school with a very sceptical view of this illness. I certainly left medical school with the idea that it was hysterical nonsense, that I was never going to see a case of it and I might as well go away and forget about it.

It was not until I was in my late twenties that I was working in a hospital and I caught a very nasty dose of chicken pox from one of my patients. I got a mild chicken pox encephalitis, inflammation on the brain associated with the chicken pox. That is how I got involved with ME/CFS. I developed this chicken pox encephalitis. I was really quite poorly with it. I could not recover from it. I got all these typical ME-type symptoms. I went round a series of doctors, trying to get a diagnosis as to what was wrong. I got all kinds of explanations. It wasn't until I met up with Melvyn Ramsey that he diagnosed my case of ME. So I have been involved with this illness now for about 30 odd years.

I work in private practice. Most of my work revolves around ME/CFS, and I have a great many hats on, I suppose, in connection with ME/CFS. As people probably know, I am Medical Adviser to the ME Association, which is the national support charity. I supervise our research fund, which I will come to in the course of the lecture. I currently sit on Professor Harrington's group which is reviewing the Work Capability Assessment, which is a very important aspect of benefit reform. I am a member of the MRC Expert Group on Research, which I am going to come to in a moment as well. That is just a few of my hats in connection with this condition.

I will mention a few bits of literature that I will refer to in the course of my talk. I have brought a few copies along, if anyone wants to buy one at the end. This is a booklet we publish at the ME Association. It is written by myself, with some help from Dr Avajit Chaudhry, who is a neurologist at Queens Hospital Romford. It is a 40-page guide, called our Guide to Clinical Issues. It basically summarises research, what doctors should be doing to assess and diagnose people with ME and all aspects of management; that is, drug treatments and non-drug treatments as well. It is all fully referenced at the back. It is primarily aimed at doctors and the medical profession.

This is a publication from Professor Harrington, which he produces each year on trying to reform and trying to get the Employment and Support Allowance, WCA, (Work Capability Assessment) into a more fair and effective shape for people with fluctuating medical conditions and with mental health problems as well. I will come to this at the end, but at the moment our Fluctuating Conditions Group have produced a report on how we think the WCA descriptors should be changed to make them more fair and effective for people with fluctuating conditions, and mental health conditions. These are about to be assessed in a medical-based review by the Department of Work and Pensions (DWP). We get the results from that at the end of the year. Hopefully, once ministers have got them we might start looking at getting a reform of the WCA.

I was a member of the former Chief Medical Officer's Working Group on ME/CFS. I think this is still a very useful report that the working group produced. We are going back now to 2002. You can still get this from the Department of Health website online. It contains quite a lot of useful information, particularly on things like prognosis and children.

The NICE guideline review on ME/CFS, which I am sure everyone is familiar with, is not something which the ME Association, like many other charities, felt we could endorse, because of the way it is advocated, really as a sort of one-size-fits-all treatment – graded exercise and cognitive behaviour therapy (CBT) – for everyone who has mild to moderate ME/CFS.

The NICE guideline review on this illness is going to be reviewed, or the NICE guideline is going to be reviewed in 2013, which has always been the intention of NICE. We do not have any firm information from NICE that it is going to be reviewed in 2013, but we are working on that assumption at the moment. You may have filled in the ME Association questionnaire on CBT and graded exercises, which we ran for three months during the summer, because we wanted to collect some patient evidence to send to NICE, in the hope that they were going to modify their

position, particularly on CBT and graded exercise. So we are hoping that that is something which will occur.

The final publication I will mention is something you can download from the ME Association website, if you want to do so for free. We carried out a survey, an online and paper survey, a couple of years ago. We got about 4,000 odd responses to this. It asked people to give their opinions on what things helped them and what did not help with their illness. It covers all aspects of illness: symptoms, pacing and CBT. You name it, it is all there. It is subdivided. You go to pain relief and there are the different drugs people have tried. So that is patient evidence on what helps and what does not help people with this illness. It has all the alternative stuff as well; supplements and vitamins and everything possible. Those are a few of the bits of paper that I might mention during the course of this presentation.

I want to talk about hot topics at the moment, which is basically what is going on in the way of research, what is going on in the way of management and what is going on in the way of benefits.

Just before I talk about research, I will talk about some background stuff to research and why people who are in the research community find this a difficult illness to research.

First of all, there is the epidemiology of this illness; that is, how many people have got it. There are an awful lot of people out there who suffer from general fatigue. If you look at studies on epidemiology, you will see that perhaps 10% of the population will experience chronic fatigue of some sort, if you ask them about how they feel, in relation to mental and physical fatigue. By chronic fatigue, I am talking about fatigue which is interfering with the normal ability to carry out normal daily life. If you then narrow it down to what we would describe as a chronic fatigue syndrome or ME, then the numbers are very much smaller.

(Slides were shown)

There is our donkey! If you want to find out about the donkey, put it into Google! This is not me, but is somebody with chicken pox, which is a pretty nasty illness if you get it as an adult, which was the point I wanted to make.

The next line shows some of my *hats*. We have gone through the publications. This is what I want to talk about: research, management and benefits. I have put these things in brackets.

The problem of researching this illness partly stems from the fact that we

have an awful lot of people with chronic fatigue. 10% of the adult population have chronic fatigue of some sort.

If we are talking about ME/CFS as a distinct clinical entity, I think we are talking about 2-5 per thousand in the population. This is just the background to ME/CFS.

You will be familiar with the symptoms of ME/CFA, but I have put them up as the background of research. Because the research being done (or is about to be done) into this illness is, if you like, symptom-based research, it stems from the fact that there are a number of different symptoms, particularly what I would record as the key symptoms, which are directing research in different directions. So there is quite a lot of research going on into the role of infection in this illness and the immune system response. There is muscle research, because people are aware that fatigue, particularly the characteristic fatigue you get with this illness, may well be accompanied by pain in the muscle. Then the important variety of brain symptoms which occur in this illness, which is again sending research off in the direction of looking at abnormalities in the brain and central nervous symptoms.

The three core brain symptoms I would say that are so characteristic of this illness are the problems with short-term memory, concentration, attention span and the way you are able to process information, which we call cognitive dysfunction, and what we term disturbances in ANS. ANS stands for autonomic nervous system dysfunction. This gets missed out of most of the definitions of this illness. Certainly if you read descriptions from doctors of it, it is very rarely included. However, I believe it is a very important part of this illness.

This is part of the nervous system, which I will come to in a moment, which controls your blood vessels, your bowels, your bladder function, but in particular your cardiovascular system (your heart). And these symptoms, which are terribly characteristic of this illness, are what we call orthostatic intolerance, which is the inability to carry out things in a standing, upright position. Postural hypotension, which is blood pressure falling when you stand up, makes you feel faint. Some people, as part of this autonomic dysfunction, have something called the postural orthostatic tachycardia syndrome (POTS), which is another part of this pulse/blood pressure disturbance, which probably stems from a dysfunction of the autonomic nervous system.

Thirdly, the other brain symptom which is terribly characteristic of this illness, is sleep disturbance. Quite often, particularly in the very early stages of this illness, people are wanting to sleep all the time, which is what we call hypersomnia. Then, as the illness goes on, there are various

disturbances in sleep pattern. You cannot get to sleep. You are awake during the night. But whatever it is, you are waking up not refreshed; that is un-refreshed sleep.

Then, as I am sure you are aware there are various other, what I would describe as, secondary symptoms associated with this illness. It is the key characteristic symptoms which are driving research into the different directions at which it is going.

Along with the fact that there are a lot of symptoms, we have a lot of confusion between fatigue, chronic fatigue and how you define the chronic fatigue syndrome. We have, unfortunately, a range of symptom-based definitions which doctors use, both for clinical and research purposes. So we have the original definition of ME from Ramsey. We have a modified version of ME, which I have produced and various people called ‘the London criteria’. We have chronic fatigue syndrome, which is defined by Fukuda, which is the American definition, and is the one used for most research. Then you widen out this CFS definition into various other definitions – the Oxford definition, the NICE definition – and you get broader and broader definitions as to who you bring into this chronic fatigue category. You also have the ME/CFS Canadian definition and we have a new international consensus criteria on ME.

The problem with all this is that we have different groups of patients being selected by research studies and clinical trials. One thing that I think we really do have to sort out if we are really going to make progress with this illness – and it is something the MRC Expert Group feels very strongly about – is that we have to start sub-grouping the people who have come under this very messy ME/CFS umbrella.

I think we missed a slide. We have different ways of describing these different things under this umbrella, and this awfully messy compromise of ME/CFS. What I compare it to is rather like taking all the different types of people who have arthritis and putting them under a “chronic joint pain syndrome”, and saying they all have the same cause and the same treatment, which is clearly crazy. Because people with an inflammatory arthritic condition like rheumatoid arthritis, you may want to treat with steroids, but someone who has got osteoarthritis (which is wear and tear arthritis) you just would not want to give them steroids at all. That would be dangerous. So we are dealing with a very complex group of patients, when we start to research this illness and, as I say, we do need to get this sorted out.

## **Research**

I do not want to go into what we know about research, but try to look

forward to what is happening with research, and where we are going with it. A lot of us, myself included, feel that this is probably a three-stage illness. I like to use the term a “3 P illness”, in which you have things which predispose you to getting it in the first place. We certainly know that there seems to be a genetic predisposition towards getting this illness, as there is with many conditions – arthritis, breast cancer and heart disease et cetera. There are things that clearly precipitate this illness. We know that viral infections are the prime thing for triggering this illness. Around perhaps three-quarters of people with this illness will very clearly predate the onset of their illness to a viral infection. But it is not always a viral infection. Some people start off with a non-viral bacterial infection.

Some interesting papers have just come out on people in Norway who started this illness with an infection called Giardia. There are some people who started with something called Q Fever. So it is not all viral infections, but it tends to be.

Then there are things that mimic infections which can start this illness. I am particularly interested in people who start following a vaccination, and in particular hepatitis B vaccination. I have probably got the largest list of people in the country who start the illness following hepatitis B.

So there seems to be some sort of start to this illness, when you put some stress on the immune system, particularly with an infection, and you get an ongoing, abnormal response to whatever sets it off. However, having said that, we have a complicated factor in that about 25 percent of people will not start it off with a clear-cut infection. Again, that makes research difficult.

## **XMRV**

I don't think we are ever going to discover a large piece of this missing jigsaw, as to what causes ME/CFS. Two or three years ago, people got very excited – I have to say I didn't get too excited; I was sceptical about this from the start. Two or three years ago there was a paper published on XMRV and it was surrounded by a great deal of hype. The inference was that this was possibly the major cause of this illness. It was going to produce a diagnostic test, and it was going to form an effective form of treatment in the form of antiretroviral drugs.

As I am sure you are probably all aware that Professor Ian Lifkin(?) produced a report on the results of the multi-centre study on ME/CFS and XMRV a couple of months ago, and found no evidence whatsoever to link this retroviral condition to ME/CFS. So I think we are now in a position where we can draw a red line under XMCV and move on.

Where things start getting more complicated – and I think this is where we are looking at piecing together pieces of a jigsaw – I do not think we are ever going to have one large piece of this jigsaw suddenly fit into place and say, “We have discovered what causes ME.” We will keep finding little bits of this jigsaw involving infection, immune system dysfunction, muscle et cetera, and piecing together a very complex picture of what causes this illness.

We know that infections can trigger this illness off, but it is very uncertain at the moment – certainly with the majority of evidence being against it – that persisting viral infection plays a role in the illness, once the infection has triggered it off.

Where there is overwhelming evidence is that there are abnormalities in the central nervous system, one of which produces what we call central fatigue. We know that people with this illness have disturbances in a tiny gland in the brain called the hypothalamus, which regulates temperature control and various other parts of the body function; autonomic dysfunction, which I am going to keep talking about. It is a very characteristic feature of ME and there is growing, robust and replicated evidence to indicate that the autonomic nervous system is involved. Certainly there is some preliminary evidence that what we call in the jargon “neuro inflammation” is involved, which is a degree of inflammation within the central nervous system. We have some evidence of muscle abnormalities, which I am going to come to. We have quite a lot of good, consistent evidence of immune system dysfunction, possibly in the form of what we call in the jargon “low level activation”. It is as though you have picked up an infection, your immune system has started to produce these immune chemicals called cytokines, which you get when you have had a dose of flu that make you feel grotty. But it may well be that that immune system dysfunction keeps going on; it does not switch itself off.

We know there is good evidence of neuro endocrine dysfunction, which is how the brain controls hormone output, and particularly the regulation of what we call the hypothalamic pituitary adrenal axis (HPA axis). This is the control mechanism that sends messages to the adrenal glands, which sit above your kidneys, to produce cortisol. We know that people with this illness have slightly lower levels of cortisol.

Then it may well be that symptoms like pain and sleep help to keep the illness going, along with these biomedical abnormalities. It is then not surprising that some people with this illness go on and develop depression. You may have stress associated with it, which will not help it. At the same point – and I will not go on to talk about it today, as I want to keep

to the biomedical model – there are some psychiatrists who believe that basically that this illness is basically a psycho-social illness, where abnormal illness beliefs and behaviours are perpetuated here. I am not going to go into that today.

That is a very quick summary of where perhaps we are with what we know about the illness in the way of research. As you are probably aware, there has been terrific criticism over the years of what the Medical Research Council (MRC) has done in relation to research, or rather what it has not done in the way of research. The Medical Research Council is the government body that sits on this great pot of money for medical research.

In response to this criticism from the charities, parliamentary groups and patients, in 2009 Professor Steven Holgate – who is an excellent chap and is an immunopharmacologist from the University of Southampton – agreed to chair an expert group. I form part of the membership of this group. We spent a couple of years – and like most things to do with the MRC, it was pretty bureaucratic. So we had lots of meetings, working groups and literature searches, et cetera. At the end of the day, we produced a list of what we felt were biomedical research priorities for the illness.

As a start – and this is quite unusual – £1.5 million [has been ring fenced for research into ME/CFS]. I fully accept it is not a lot of money, but to actually get £1.5 million of ring-fenced funding out of the MRC for a specific illness like ME/CFS, when it has expressed no real interest in looking at the biomedical side of this illness in the past, was quite a degree of success.

In December 2011 five grants were awarded. In October 2012, which was only a couple of weeks ago, as part of the momentum to keep this going we had a meeting with Steven Holgate at the Royal Society of Medicine. We have decided now to set up a UK ME/CFS collaborative, which will be an ongoing group – a much wider group – which will bring in research-funding charities and other research-funding organisations – new researchers, existing researchers, people from the pharmaceutical industry – everyone who really ought to be involved in getting research, and research infrastructure, into this illness moving forward in the UK.

Professor Holgate – and you can go to the website for this – has already set up a very successful UK research collaborative for respiratory disease. The website for that is on the thorax website. That functions very well and has brought in new funding and new people. So that is a very important latest development in the MRC Expert Group.

We set about thinking what are these research priorities that ought to be

moving forward. These are the things we identified. We go back to autonomic dysfunction, cognitive dysfunction, problems with memory, concentration and fatigue. Fatigue is split into brain fatigue, which is a very common phenomenon which you get in other neurological and inflammatory conditions.

If you speak to people who have rheumatoid arthritis, multiple sclerosis, Sjogren's Syndrome, primary biliary cirrhosis, they will describe the overwhelming fatigue that they have with their illness. This is a general fatigue, not like the peripheral muscle fatigue that forms part of ME, but it is a very central component.

So we want to look at both central brain fatigue and peripheral fatigue, which is the energy-induced muscle fatigue. We want to do more work on immune dysfunction and immune dysregulation – in particular, things like natural killer cells (cytokines) – and to look at neuro inflammation within the brain, pain, sleep and developing interventions. These are drug treatments which might be involved in looking at cytokine inhibition; that is, dampening down the cytokines that are produced as part of this overactive immune response. Then the treatment of specific symptoms, particularly in relation to pain and sleep and access to blood and tissues for research, which is very important.

I go back again to the autonomic nervous system. It is a complex part of the nervous system. In very simple terms, *here* is your brain and central nervous system. The long yellow nerve going down your back is your spinal cord. Then coming off the spinal cord are these vast amounts of small nerves which go to every part of the body. Particularly in relation to ME and the autonomic nerve system, these are nerves that go to your heart, lungs, stomach, gut, bladder and bowels and control their function. They either speed up the function of the bladder, bowels or heart, or they slow it down. Particularly in relation to your heart, blood vessels and blood volume that circulates round as a result of your heart function, if your autonomic nervous system and the instructions it is sending to your heart are not producing the right responses – particularly when you stand up – you are going to have problems. We feel that [is] part of the problem.

One of the symptoms of autonomic dysfunction in ME is orthostatic intolerance; the problem of standing up, feeling faint when you stand and blood pressure falling when you stand up. When you move from a lying position to a standing position about 700 mls of blood goes straight to your legs. If your autonomic nervous system is not sending the right instructions to your blood vessels to tighten up, and to your pulse to increase to get blood circulating round to the brain, you are going to feel faint, you are going to feel 'off' when you stand up. So it is very important that we investigate further the role of the autonomic nervous

system.

We have a lady called Professor Julia Newton at the University of Newcastle – and who I was with last week. She has done more to look at the ANS in relation to ME/CFS than anyone else, certainly in the UK and possibly anyone else in the world. She has got one of these MRC grants so she can look at what effects the ANS dysfunction is having on pulse and blood pressure; particularly what effect this is having on cerebral hypoperfusion. This is changing posture and loss of blood supply up to the brain, so you feel woozy and faint. So a group in Newcastle are going to compare a group of people with ME/CFS who have evidence of ANS, and those who do not, and also a group of very sedentary controls, just to show that this is not simply due to inactivity and decondition, which some people, some doctors, will criticise these sorts of abnormalities as being.

The second study from the MRC – and I was with Dr Ng at the University of Newcastle last week – is to see if we could find a biomarker for chronic fatigue. Dr Ng runs a register for people with Sjogren's Syndrome, which is quite an interesting condition and which has quite an overlap with ME/CFS. These people have dry eyes, dry mouth, dry respiratory tract, joint pains and also overwhelming fatigue. It is a very carefully defined syndrome. So it is not like ME/CFS. If you have Sjogren's Syndrome, you have the symptoms, you have the blood tests and you know you are dealing with people with Sjogren's Syndrome.

Dr Ng has 550 blood samples nation-wide from people with the illness. There are other overlaps with ME/CFS. It is a female-dominant illness. It is an autoimmune illness, and it probably has the same sort of prevalence as ME. He is going to look at all kinds of proteins and metabolic markers in the blood to see if he can find, starting off with the Sjogren's Syndrome people, a marker for debilitating fatigue in this illness. Then this work will be extrapolated into a group of ME/CFS people, so let us see if we can find a biomarker for fatigue.

I talked about the role of immune dysfunction in this illness, and the role of these chemicals called cytokines. If you remember, these are the chemicals that you produce when you have a flu-like infection. One of the things that also happens with cytokines and these immune chemicals is that they can be given as a treatment for certain types of illnesses. One of the illnesses that they are given in is using Interferon Alpha is Hepatitis B.

At King's College Hospital, 100 people with Hepatitis C infection, are being treated with Interferon Alpha – so this is a drug which is an immune system activator, which will often lead to fatigue, flu-like and ME-like symptoms – and are going to be followed to see what happens to their biomarkers in the blood before, during and after treatment. So their

cytokines, hypothalamic pituitary axis profiles and things are going to be measured and compared between the groups who go on to develop a ME/CFS-like illness, as a result of their immune system-activated treatment and those who do not.

Then we might then start to look at the roles of drugs – there is one called Etanercept, which is possibly being trialled in Norway – which can dampen down this overactive immune response. So that is the role of the immune system and pro-inflammatory cytokines.

The peripheral fatigue that people with this illness have – as I know very much personally – there are parts of your muscle called the mitochondrial, and these are your Duracell batteries within your muscle cells. That is a diagram of a muscle mitochondrial.

About 20 odd years ago I did some work that we published in *The Lancet*, with Professor George Radda, who at the time was working at Oxford. We looked at my muscle – Professor Beard also took some pieces of muscle out, so I have a nice scar above my leg – to look at my mitochondria and to also look, using magnetic resonance spectroscopy, to see how the mitochondria within the muscle were actually producing energy. We know from these experiments, and we know also from the work that Professor Newton has done up in Newcastle, that certainly some people with ME/CFS, when they exercise produce more acid within the muscle, and they do not get rid of it as efficiently as normal people do. So they have an acidosis, a prolonged and more severe acidosis within the muscle. So we want to look at what is happening within the muscle, particularly these Duracell batteries within your muscle, the muscle mitochondria.

The fourth grant from the MRC has gone to Professor Anne McArdle at the University of Liverpool, looking at mitochondrial damage. She is an expert at looking at what happens structurally within the mitochondria. This may well lead to therapeutic interventions, which can help to improve the function of your muscle and your muscle mitochondria.

The final MRC study will be on sleep, which is a major component of the illness. Professor David Nutt at Imperial College, is looking at the relationship between sleep, in people who cannot sleep properly, and fatigue – particularly in relation to what we call slow wave sleep disturbance, and the loss of what we call deep restorative sleep. Part of the research at Imperial College will be to use a new treatment called sodium oxybate, which is a drug which can enhance slow wave sleep, in a group of people with ME/CFS and a placebo group. It is interesting that this drug has been used in the treatment of fibromyalgia syndrome, and there is a Belgian trial due to start as well using it. So there are further

studies on sleep disturbance in this illness and a therapeutic intervention.

So that is a flavour of what the MRC is funding at the moment and is about to start taking place.

We, at the ME Association, along with ACME(?), ME Research UK, and a private donor, have set up a biobank at the Royal Free Hospital and the University College London. This has now been running for about a year. We have collected about 60 to 80 blood samples from people with very, very well-defined ME/CFS. We have a vast amount of clinical data on these people, their investigations, their clinical symptoms and examination findings. It is all there. So all this information accompanies these blood samples. We have just arranged funding for a further year of the biobank at the Royal Free. It costs £160,000 to set up. It is costing us about £160,000 to keep it going for a second year. In the second year, now that we have these samples here, we are hoping to get another 100 samples, which will mean that people who want to do research on the illness will be able to do so, just requiring blood samples. They do not have to go and find patients with this illness, and collect lots of clinical data, and go through all the hurdles and hoops, when they do not even have patients coming in to their hospital with this illness. The patient data and blood samples will be at the Royal Free for them to use. And they will also be able to co-ordinate with other blood sample biobanks in other parts of the world, if they wish to do so.

Another thing I am particularly involved with – and we have published a short paper on this in the *Journal of Neurological Sciences* – is what we call the neuropathology of this illness, which is what is going on in the brain/spinal cord, and in particular: is there inflammation? One thing we have found so far in really just a small number of post mortem specimens – four in all, and it is in some of these – is something called dorsal root ganglionitis. The dorsal root ganglion – which are bundles of neurons which sit outside the spinal cord – the big nerve transmitting nervous information right down to the tip of your toes from the brain – are junctions of nerve fibres sitting outside the spinal cord, so they are in what we call the peripheral nervous system. These bundles are where nerve fibres come in with what is called sensory information – this is information about pain, sensation, touch and movement – before this information is transferred up the spinal cord to the brain. What has been found in a small number of these post mortems is inflammation within the dorsal root ganglia (dorsal root ganglionitis).

It is interesting to note that this is an abnormality you find in Sjogren's Syndrome as well. In Sjogren's Syndrome, dorsal root ganglionitis has been associated with what we called peripheral neuropathy. This is pain, abnormalities and sensations in the arms and legs. We need to do more

work on this, and we need more specimens, but it may well be that part of the explanation for pain, sensory disturbances which occur in ME/CFS, could be due – as they appear to be in Sjogren's Syndrome – to a dorsal root ganglionitis. That is definite evidence of neuro inflammation in this illness and is quite an important finding.

Let us move on from research. I could talk for ages about management, and I am conscious of the clock. I will whizz through the slides, so I can talk about management issues in Questions and Answers, but I will pick up on one or two on management.

First of all, before making a diagnosis of ME/CFS it is extremely important, going back to my original science, that we consider (or at least a doctor considers) all the different illnesses which can produce a collection of symptoms which are much like ME/CFS. If you have a copy of the purple booklet, or the paperback booklet, or any of these guidelines on ME/CFS, you will see that doctors are recommended to do this – and which I think is absolutely essential – before a diagnosis of ME/CFS is made. So all these (Slide shows list\*) It is essential. These are all in the purple book, and some are in the NICE Guidelines. They are not all in the NICE Guidelines. The NICE Guidelines are a bit defective, but they are around generally to find. It is essential that this list of routine investigations is done in everyone before diagnosis is made. So you are ruling out liver problems, kidney problems, thyroid problems and primary muscle disease.

An important one is to do a simple screening test for coeliac disease. Because irritable bowel syndrome plus fatigue should be raising a query in the brain: is this actually coeliac disease and not ME, with someone who has got fatigue and irritable bowel? That is a relatively easy thing to do, and it is not an uncommon misdiagnosis of this illness. So routine investigations are terribly important.

Then there is a whole range of other investigations. Again, they are all in detail in the purple book, in some circumstances. So if you have someone who has got more symptoms, what we call red flag symptoms, or more joint pain than you would think is perhaps consistent with ME/CFS, you need to go down these routes and make sure there is not Sjogren's Syndrome or primary biliary cirrhosis, where you have skin irritation and slightly abnormal liver function tests. So you make sure the diagnosis is correct.

### **Management of people with ME/CFS**

I will pick out one or two. Very controversial is graded exercise and pacing. I am happy to discuss this more in question time, but we are in

this awful position with the NICE Guidelines saying everyone with mild to moderate ME should be given graded exercise and/or CBT. I think the only way you are going to be able to challenge this – because there is no research being done, or what I call satisfactory research done on pacing, which is obviously the form of activity management that most people with this illness appreciate – is to provide, certainly the NICE Guideline next year, patient evidence which (1) shows that most people with this illness actually prefer pacing and find pacing more effective, and (2) to what extent they do not find graded exercise effective and to what extent graded exercise makes them feel worse.

We know from the MEA management report which I referred to there, and which you will find on our website, that from graded exercise 22 percent felt they improved, 22 percent said there was no change and 56 percent actually felt worse.

From pacing, patient evidence showed 72 percent improved, 24 percent had no change and only 4 percent were worse. So there is clearly something going wrong here, when you have one official guideline recommending a form of treatment called graded exercise, and the patient evidence saying: “No, hang on. What we found more effective is pacing. And, in actual fact, many people find graded exercise is making them worse.”

I am happy to go into that in more detail in Q&A.

The next slide is CBT. Again, the patient evidence is not the same as what you are getting from the randomised controlled trials, which is what NICE uses as their gold standard.

So far as management is concerned and drug treatment, we do not have any drugs which have been shown to be effective at treating the underlying disease process in this illness – whatever that is – but we do have a certain amount of some drugs which can help in some circumstances, particularly symptoms such as pain, sleep – sometimes with autonomic nervous system dysfunction – but that is a very specialised area. Irritable Bowel Syndrome, if that is co-existing and depression, if that is co-existing.

So far as pain is concerned, I quickly mention that over-the-counter painkillers (aspirin, paracetamol, ibuprofen) in my experience tend to be relatively ineffective for people who have significant pain with this illness. There are things worth trying, from the point of view of prescription-only drugs – particularly a low dose of a sedating, tricyclic drug like amitriptyline, and possibly moving on to one of the types of drugs that are normally used in epilepsy, but are used by doctors who treat people for

chronic pain, one of which is, Gabapentin. I know there are people with really quite severe pain – sometimes pain is the most important aspect of this illness – and they have gone on to opiates and morphine-type treatments.

I will not go into symptomatic relief any more at this point, but I would be quite happy to deal with that in questions.

Drug treatment at the moment is very much confined to what we can do for symptoms. Can we treat the underlying disease process at the moment? The answer is simply no. We are looking at various things, and this goes back to the various parts of the research jigsaw I was talking about. There may be a role for antiviral medication. As I say, the role for persisting viral infection in this illness is uncertain. There is certainly evidence that certain types of virus – human herpes virus type 6, Epstein-Barr virus – may be reactivated in this illness. A drug called Valacyclovir may be effective in some patients where this is occurring.

There was a further paper from Jose Montoya(?) over in the States which came out last week and is on the MEA website, if you want to look at it. Again, it has a role for damping down this over-immune cytokine response, with cytokine inhibition, which I have talked about. We have low levels of cortisol in the illness from the adrenal glands. But the evidence at the moment is that cortisone and steroid treatment is not a form of treatment that we want to go down – certainly thyrotoxicosis (Inaudible due to coughing)...would be no abnormal thyroid function tests. Then there are a range of drugs which can be used for people who have, what we call in the jargon central fatigue, brain-induced fatigue. Norfranil is one that is used for people with narcolepsy, which is people who suddenly go off to sleep during the day. There is one small trial which has used this drug in ME. We are suggesting that there is some benefit there. Then we have clinical trials going on over in the States with Ampligen and this interesting trial with Rituximab.

Rituximab is certainly the drug of most interest at the moment. Most people here have heard of it. We go back a couple of years or so to a small group of doctors in Norway. Two of them who are oncologists, who treat people with cancer, have two patients with Non-Hodgkins lymphoma. They gave them the treatment with Rituximab and it was very successful in relation to the treatment of their lymphoma. But they also noticed that people with ME/CFS also made a significant improvement in their ME/CFS. So they decided to do a further trial on this, and that is the paper which came out recently on this. They treated 30 people with ME/CFS with a placebo and 30 with Rituximab and there were significant benefits.

Rituximab is an interesting drug. It is what is called an anti CD20 antibody. It causes depletion of a part of the immune system called the B cells. It causes B cell depletion. What may be happening is that you are getting rid of your B cell population, or to a large extent getting rid of it. The B cells are cells within the immune system which produce what are called auto-antibodies. These are antibodies which attack part of the body. So you are removing this auto-antibody component in ME. It is, however, possible, going back to the other finding that we know people have, reactivated viral infection (particularly herpes viral infections) that Rituximab might be dampening down or removing some evidence of this reactivated viral infection. On balance, I think it is more likely to be an immune system effect of this drug.

Anyway, here we have this drug, which is normally used to treat lymphoma. There is a significant response in people with ME, in a really well conducted, randomised controlled trial. The problem – why you cannot get Rituximab at the moment to treat ME – is that, first, it is a very expensive drug. Second, it has a potential to cause very serious side-effects. Some people have even died as a result of taking Rituximab, so it has to be taken very, very carefully. And we only have results in one small clinical trial at the moment. Until we have the trial replicated, and we have more results, there is no way that a drug like this is going to be given to people with ME, but it is an exciting find.

I have been doing my utmost to get a replicated study going in the UK – so far without success, which is very disappointing. I was over in the States in June with a group of colleagues, trying to see if we could set up an international trial to get Rituximab looked at again. So here we have a potentially very exciting and unusual form of treatment, but it does need work; it needs further study. It costs money and we need to find someone with good experience of this illness who has got a good team together, who can work with a drug like Rituximab who can put this clinical trial together, and I hope we are going to see that.

I am conscious that we are well over time, so I will quickly close with the Department of Work and Pensions (DWP). There is Mr Iain Duncan Smith, who I occasionally see on my very regular visits to Caxton House, which is the headquarters of the DWP in London.

I am working with a group of people who represent other illnesses called fluctuating medical conditions, which have a considerable degree of overlap with ME/CFS. So these are people who deal with people with HIV/Aids, rheumatoid conditions, Parkinson's disease, MS and inflammatory bowel disease (Crohn's Disease, ulcerative colitis). We all have one problem in common: our illnesses fluctuate. You cannot take a snapshot of what you can do at that particular point in time and say,

“Because you can walk this distance, or lift that, or bend over” or whatever, “you can do it reliably, repeatedly, safely and in a timely manner.”

One thing we are hoping, because we have used the words repeatedly in our report – and it is very nice to see Lord Freud using them in a statement in the House of Lords as well, in relation to benefit assessment – is that we all want the WCA descriptors to be revised. We have produced reworded descriptors to cover all the descriptors which, as I say, are about to be tested. But whatever task you are being asked to do, whether it is movement, lifting or bending – whatever it is – you have to be able to do this reliably. You have to do it repeatedly, in other words you have to do it repeatedly throughout the course of day, not on a one-off basis. You have to do it safely, in relation to yourself and others, and you have to do it in a timely manner. There is no use saying you can walk 50 yards or 200 yards, provided you have half an hour to do it. You have to do it in a reasonable amount of time. So we want to reword the descriptors and insert these very key words into it.

Our report on this, if you want to download it, was produced over a year ago. It went to the DWP and accepted by them. It was accepted by Professor Harrington, and was slightly modified by a scrutiny group appointed by the DWP. For the past three months I have been up and down – almost every week at times – to the DWP working with my colleagues with the other diseases, making further modifications to our recommendations. That work is finished and the revised descriptors we have proposed are about to be tested in an evidence-based review by the DWP, in comparison to the current descriptors. That will take up to Christmas. The results will have to be analysed and the report prepared. This will not produce any immediate changes to the support allowance, and the WCA assessment, but hopefully at some point next year, when we are back from this assessment and ministers are going to sit and seriously look at the WCA, it will make changes to the WCA.

The other thing that we have recommended, which has not been taken on board at the moment, but it has been accepted by Professor Harrington as being perfectly reasonable, is that we feel there should be a new descriptor to cover the issue of fatigue, and also a descriptor that covers pain, which is a serious gap in the system at the moment.

Having said that, I still believe that the Work Capability Assessment is not a satisfactory method of assessing people for work, but our remit was to look at the WCA as it currently is and to make recommendations on it which will make it fair and effective for people with fluctuating conditions.

I have to say there is a group which we now work with who have done the same in parallel with the mental health descriptors. In our revision of the descriptors we have integrated the mental health descriptors in the WCA with the medical descriptors, because there are a lot of mental health descriptors which are not totally applicable to people who have mental health conditions. They are problems, particularly if you have problems with cognitive dysfunction, and you should be picking up points on the mental health descriptors. So by integrating them, we are hoping to overcome that problem as well.

I think I will leave further questions on ESA and benefits to question time, because I am pretty heavily involved in this and am happy to take these questions. We are dealing with the ESA 50 form, Atos medical assessments. We have had meetings with Atos, both with the fluctuating conditions group and with representatives from the House of Lords a couple of weeks ago.

I will finish with passing on some tips, if you are involved with Atos, or are going through an appeal procedure, because you have been turned down for ESA. First, it is vital that if you can – and we fully appreciate the difficulties of being able to – obtain medical evidence. You may not have a GP who you are seeing. You may not be under the care of a consultant. You may have to pay for it. If you can provide additional evidence from either your GP, consultant or any health professional seeing you, that will be very helpful in supporting your case.

If you are going to an Atos medical you can ask for a recording of that interview assessment. You will probably find it difficult to get one, but you are entitled to ask for one and you should be able to get one. This is an issue we brought up at the House of Lords a few weeks ago. You can take a companion with you who may be able to provide some useful information.

If you are turned down for ESA, or put in the work-related activity group, and you want to appeal then get a copy of your Atos report. You do not get it automatically from Atos. You have to get it from the DWP, because it is their property. If you are not happy with the way you have been assessed – either by Atos or even on appeal – then make a complaint. If you are making an appeal, turn up in person. You significantly increase your chances of success at an appeal, in relation to benefits, if you turn up. Do not just leave it to them to look at the paperwork. There is a very nice video which has been produced by Dr Jane Rainer, who is the Chief Medical Officer person at the Ministry of Justice Department that deals with social security appeals. We have just put it on MEA website. It is a very simple step-by-step guide as to how you go through and what happens at an appeal service. It is important to remember that the appeal

service comes under the Ministry of Justice. It is separate to the DWP.

That is an advert for the ME Association. We have lots of literature that you can order via the website. We have an ME Connect Information Support Service which is available seven days a week. It is not every hour of the day, but it is available for quite a few hours of the day. If you want to talk to someone about the illness, we have volunteers available seven days a week. We obviously do a lot of campaigning on benefits and services et cetera.

We form the secretariat to the All Party Parliamentary Group on ME. I was with them last week discussing what we need to talk about at Westminster, in relation to this illness over the coming year. We will have a meeting later in the year on severe ME. We then want to have a meeting on benefits early in the new year. Hopefully we will help launch, by way of a reception at the House of Commons, the UK Research Collaborative on ME, which I was talking about earlier.

That is our website and we have a very active Facebook page, if you wanted to join discussions or post messages for help, information or whatever.

### **Q&A Session**

Q Recently there has been an idea about hypermobility being part of the problem with ME. I know within our group there are two people who have been diagnosed with hypermobility and ME.

A I don't know whether you have seen it – you can Google it and find it – but I referred to it in the purple booklet. I can't remember if I put the reference to it, but there is an overlap between people who have what we call hypermobility syndromes; people who have very mobile joints. It is also called Ehlers Danloss Syndrome.

Q Is that exactly the same thing?

A It is. There are various hypermobility syndromes and that is one of them. There is an overlap between ME/CFS, and people who have these hypermobility syndromes may have quite debilitating fatigue.

Q Would it be defined as Ehlers Danloss or ME? It seems to me there are certain illnesses that you can stick on to ME, like fibromyalgia, and there are other illnesses which are ---

A There is an overlap with IBS and this illness. There is an overlap with migraine and with fibromyalgia. I think particularly in adolescence there is a degree of overlap with Ehlers Danloss. I did have a patient

support group for people with hypermobility syndromes. I was with a chap from that support group who came along to one of our parliamentary meetings at the House of Commons. I think they also have this autonomic dysfunction as well with hypermobility syndromes. To use the common phrase, it is an area where more research needs to be done. Having said that, the vast majority of people with ME/CFS do not have hypermobility. They do not have that sort of joint mobility that is seen in hypermobility syndrome. If you want to follow it up, I think the reference actually is Ehlers Danloss, rather than hypermobility. Put it into Google and there are one or two papers on it which have come from people in the States.

Q Is there any link between subarachnoid brain haemorrhage and ME?

A I would say no. I think the simple answer is no.

Q Thank you.

A People not familiar with subarachnoid brain haemorrhage – and I haven't seen one since I was in hospital medicine in the neurology department at the Middlesex ---

Q I am very confused at the minute whether I have got ME or not. Someone has mentioned thyroid problems to me, and adrenal gland problems. It seems that all the symptoms overlap with each other. It is like a minefield.

A One of the things I put up on the screen, which we didn't go into in any great detail, is the way in which somebody needs to be very thoroughly assessed – and you cannot do it in ten minutes in the GP surgery – before coming to the conclusion that you have got ME. In quite a lot of cases it is relatively straightforward. You get someone like me with a personal history of being a perfectly fit young adult – never had any sort of illness in his life – who gets chicken pox and doesn't get over it. Well, the chicken pox goes but then you are physically knackered after doing even the most minimal amount of physical activity. You are mentally knackered when you do mental stuff. You are off balance. You have alcohol intolerance and you feel flu-like symptoms all the time. To any normal doctor that should be setting off alarm bells: this is ME/CFS, unless told otherwise. That would be relatively straightforward. But not everyone is straightforward like that.

As I say, about a quarter of people who present and do eventually get diagnosed with this illness, do not have a clear-cut infective onset to their illness. So if you fall into that category, then you would be wanting to do a rather more exhaustive search for other possible causes. As I say, equally, if you have other symptoms which either do not normally tie in with ME – say you have skin itching or something, that would suggest something else is going on – even though you may have all your other

ME-type symptoms. If you have someone with skin itching, the first thing that would strike through my mind is: have they got this illness called primary biliary sclerosis which can cause an ME/CFS-like condition? So you have dry skin – you would be thinking: that is not a symptom of ME. Has the person got low thyroid? There is a table in the booklet with I think about 60 different conditions there which, over the years, have all been misdiagnosed as ME, because they have ME/CFS-like features as part of the condition. So you do need to have all these routine blood tests done, and other tests done, depending on what other symptoms you have. But it should be fairly straightforward to rule out whether your thyroid is normal or not. Certainly a low thyroid can produce a lot of ME/CFS-type symptoms. And if there is any suggestion that your adrenal function is low – which is called Addison's disease, then there are tests you can have for that. What is called a short synactine test, which would be done in hospital, to look at your adrenal function in more detail. Is it your GP who is scratching his or her head about the diagnosis at the moment?

Q They are not helpful at all. I have seen different ones all the time. Basically there is no continuity and they think I am making it all up basically.

A So you have not been referred on?

Q I was referred to what used to be the Homeopathic Hospital and also Hillingdon. But no sort of in-depth – I told them all my symptoms, but ---

A You have been to a hospital-based, ME/CFS clinic?

Q Yes.

A What have they said: yes or no or don't know?

Q They have said yes and the homeopathic hospital said yes, but I am still not 100 percent unsure if I have it, because I have never had my adrenals checked. I have never had my thyroid checked.

Q You must. I would say to go through your GP referral process and then to go to a hospital clinic. I would be very, very surprised – and I would say I would be horrified – if you had not had your thyroid function tested.

A I have, but they were the bog standard bloods tests you get at the doctor, which does not give you an in-depth-enough thyroid test.

A It depends. That is another topic. If you have your TSH and your T4 checked, and you do not have thyroid symptoms, you may want to do thyroid antibodies and one or two things. But without going into your individual case history in great detail, I would query whether you would need further thyroid function tests doing. At the end of the day, if you have a GP who, from what you have said, sounds as though is not

particularly knowledgeable about this, or experienced in this – you have been to two hospital services, and you are not overly happy with the outcome there, my feeling, if you want to pursue this – probably the only way to do so, if you can afford it, is to see someone private who is reputable – and there are not many people in private medicine in this area that I would recommend. We have been talking about one in particular, as we are in London. I am quite happy to mention his name. Tony knows him. There is a consultant in infectious diseases, Dr William Wier, who I have been involved with for many years on things. We have done legal cases together, insurance cases and whatever. William is very good. He is very nice. He is very understanding. He is not there to sell you expensive tests and treatments that you do not need. And if you want to go and see someone like that, who is going to be able to spend a bit of time with you and go through everything, I would probably, if you can afford to go private, suggest you go see and William. I don't have his telephone number with me, but I think he is still at 10 Harley Street. Tony will know.

Q I was thinking of going to see him, because I got referred to Green Acres in Hillingdon. It was quite an unbelievable assessment. Because I decided to withdraw from the CBT GEP programme, I didn't get a diagnosis. So I am going to get my GP to write.

A I am familiar with London, but not with ME referrals round here. Hillingdon...

TONY: Hillingdon is the local ME Clinic for West London.

CHARLES: Who runs the service at Hillingdon?

TONY: One of the problems is that it is not doctor-led. It is OT-led. They pull in a neurologist, who is there occasionally to do the assessment of anybody who has not had a proper diagnosis from a GP, but he apparently spends very little time.

CHARLES: I was up in Middlesbrough last week and they have a physician-led service there. The physician in charge is an infectious disease consultant, and they have other physicians in a physician-led service. In addition to that, they have other people – a nurse called Amanda McGough, who I know very well and is very good. I would not say it is “absolutely wonderful”, but it is an example of what I think should be available to anyone throughout the UK, and you should not have to go through postcode lottery. So it is basically CBT and GET.

TONY: It is not that bad. They do not push things. And the OT is very nice and very sensible and now actually extremely knowledgeable about ME, but it is inadequate. The fact it has no medical assessment involved

means it is inadequate.

Q When we sat on the criteria, that was one of them; that they were properly diagnosed before they got access.

Q But that fell apart.

A A lot of services that have been set up and normally – and I have been involved with doing one for the Wareham clinic many, many years ago – they draw up a protocol for the GPs to follow so that, to a certain extent, people have been already been screened to make sure they have not already got liver, kidney or thyroid disease, before they end up at the clinic. So they say, “Have all the bloods tests” that I put up on the screen “been done?” before Mrs X turns up at the clinic. So you are turning up, to a certain extent, with a working diagnosis of ME/CFS.

Q That clinic request that you send up all your blood work, so he had all the blood work in front of him. He actually said, “It doesn’t matter what we call it.” So that was the level we are talking about.

Q Can cortisol treatment be effective?

A There are two or three studies which have looked at low doses of cortisol treatment – and it is very low levels with cortisone. The reference is here in the purple book, if you want to follow them up. One of them found some minor benefits, the other one did not. But the problem with it is, I think on balance, because you are not getting very significant improvements with it – at the same point, you are in danger of disrupting this sort of feedback mechanism still further – and that it is not a treatment, in our current state of knowledge, that should be prescribed. So I would never prescribe cortisol treatment

Q I have been on it for three months at the moment (5mg), and there is a subtle difference. But the studies I have seen – and I have to admit, they are on the internet, and doctors hate about minions on the internet are daring to think about this sort of thing – they were talking of 15 mg. 5mg in the morning maybe 10mg in the afternoon?

A The studies have used – what are you on?

Q Hydrocortisone.

A When you said 5 mg I wondered if you were on Prednisone or Prednisolone, which is a higher dose of that. I mean, it is a very low dose of Cortisol. I mean, you can get little pellets for mouth ulcers, which are small amounts.

Q Is it worth me asking them to up it, when I see the endocrinologist or not?

A That has to be his or her clinical judgment. This is an

endocrinologist who has put you on this treatment for ME/CFS. Is that right?

Q I have had it for 22 years, and I have tried practically everything known to man and beast.

A My point is that in our current state of knowledge, I go along with the vast majority of colleagues, that this is not a treatment that – I don't prescribe it. I don't take it myself. I have not taken it myself. I think at the moment, because of the possible dangers outweigh the possible – it is like all events, do the dangers outweigh the benefits, and at the moment I think the possible benefits do not outweigh the possible defects of it. You will find occasional doctors who are prepared to give it a try. It is a shame that we are basing this information on just two or three clinical trials which were done now many, many years ago. As I said, when we talk about a background to all the business with clinical trials and research, the trouble is that we are taking a very wide spectrum of people, with different clinical presentations and probably different pathological things going on. And we are not picking out, particularly in the format of treatment, antiviral drugs or whatever, subgroups of people who may be responding. It is not subtle enough, what we are doing at the moment, to pick out both abnormalities and ---

Q I am not crashing out as badly, which is quite nice. Thank you.

Q Could you say something about supplements please? I am reading *this* (Indicated a book)

A First of all, I am not a great fan of supplements: (1) because I think they can be quite expensive; and (2) because I am not convinced there are any actual deficiencies in this illness, which have been shown with any degree of research, to be things that you need to take supplements for. So I don't take supplements. I don't prescribe supplements. As I say, I am not convinced supplements are the answer to this illness.

Q It is an answer, but it may be a support, because in here two experienced cardiologists, with a lot of experience, talk about mitochondrial of the heart and there are certain things that, with their experience, that are effective.

A There are things, I think particularly in relation to mitochondrial dysfunction, where some sort of supplement may play a role. One supplement which has a bit of evidence to support it in this illness is Carnitine. The studies are there in the purple book. There is some limited evidence that taking a Carnitine supplement may help some people with ME, but the evidence is not very strong. So in our current state of knowledge, I do not feel there is sufficient evidence to recommend to people that they actively go out and buy and take supplements for this.

Q Is there sufficient evidence that it is not helpful?

A Well... providing you are not taking anything at a high dose, or something rather dubious that could be causing harm, there is no harm in taking supplements. There is no harm in trying Carnitine, if you want to give it a try. But I am not convinced – like most of my colleagues – that the evidence is there for supplements, as a form of treatment in this condition. I am not opposed to carrying out research, and looking at things like Carnitine, and other things which might help with mitochondrial dysfunction – one of the things Professor Julia Newton in Newcastle, is doing, who is still doing bits on muscle research. She is actually taking some muscle biopsies and using cells which are grown from these biopsies from people with ME/CFS, then trying out some drugs on those biopsies. As I say, there may be a role for supplements in this condition, but I am not convinced there is anything there at the moment. The one thing I am quite keen on – and I did not mention this. I think it is quite important, particularly for people who are at the severe end of the spectrum – who are not getting outside and are not getting out in the sunlight, daylight and may be on restrictive diets and are relatively inactive – and that is vitamin D deficiency. There is already some evidence of vitamin D deficiency in this illness in the more severe category of people. And if you are moderately severe or housebound largely with this illness, it is well worth having a vitamin D blood test done, then considering whether you need a vitamin D supplement if your vitamin D level is low.

Q I have heard it said that probably 50 percent of the UK population is low in vitamin D.

A Yes. There are lots of studies coming out at the moment showing a vitamin D deficiency in quite a segment of the UK population.

Q I wanted to ask about the Ginkgo and Q0. They are always talked about.

A Again they are supplements which are very widely variable, very popular and claim to help with brain function, muscle function whatever. But the evidence, such as it is, is just not there at the moment. There is no harm in trying them. We have an MEA information leaflet on all these what I call muscle energy supplements, which is Carnitine, NADH Q0. There are a couple of others which I forget at the moment. But if you review the evidence, it is not there at the moment, but by all means try one, if you want to try them. If I was going to try one, I would try Carnitine personally. It is in the purple booklet, if you want to chase it up. There is evidence from some research that there is maybe a carnitine deficiency in ME/CFS. There is one study which has shown some benefit from a carnitine supplement, but it is not what we call in the jargon “robust consistent evidence”. It is very low-grade evidence.

Q Somebody recommended low dose naltrexone to help with fatigue for ME and MS sufferers. Are you aware of it?

A That is a treatment or flavour of the month almost, low-dose naltrexone. This is basically a drug which is a morphine, opiate antagonist, which is not normally used for conditions like this. There are claims from people who are enthusiastic about it. It is treatment for various autoimmune disease, like MS, and Crohns I think has been suggested as something else that you might treat low-dose naltrexone with. Certainly the evidence base is not there. There have been no clinical trials done on this form of treatment, in relation to ME/CFS. I keep getting asked about it. Our anecdotal feedback, like most speculative forms of treatment, is pretty mixed. Some people say they have improved on it, some say no change and some people say they are worse on it. So there is evidence no evidence from clinical trials. The anecdotal evidence is fairly mixed. And there are reasons one has to be fairly cautious in using something like that, because it does have a range of potential side-effects, which could interact with ME symptoms. So it is not a drug that I personally would prescribe, or have any thoughts of trying it on myself. But it is a prescription-only medicine. You will have to get it from a doctor, or – I gather, I haven't chased it up, but I gather there is some sort of internet-based doctor service, that does prescription-only drugs that is willing to prescribe it.

Q A chap in Scotland.

A Yes. Personally I think it is a bit dodgy, prescribing something like low-dose Naltrexone to someone you have never seen. I do not feel particularly happy about that, but apparently you can.

Q Dr Chris Steele. I have watched the YouTube clinic clip of Dr Chris Steele. He is trying to get it ---

A Yes. I see advertisements for some miracle new knee treatment in the Daily Mail as well.

Q It works. I am using it. Apos treatment. It is brilliant.

A Well *there* is an anecdotal report! (Laughter)

Q It is very, very expensive though, unless you are with BUP.!

A I think you would find considerable difficulty in going along to your ordinary GP and asking them to prescribe it.

Q I guess what interested me, what Chris Steele says about it – if I remember correctly from the YouTube clip, is he is trying to push it in the laws/in the Lords(?) to get it prescribed easily over here – and it has not been prescribed apparently. There are side-effects.

A Drugs cannot be prescribed, in the normal course of events, until they have a product licence for a specific condition. We are going back to

Rituximab – the only way doctors are going to be able to prescribe Rituximab – is when we have got the results from at two or three clinical trials – at least two or three big clinical trials – saying, “This drug works in ME. These people are not having nasty side effects. No-one is dying as a result of taking it. Blah, blah, blah ...” You are not going to have low-dose Naltrexone available until clinical trials have been done, and it has been found to be safe and effective, and that takes time and money. So the only way you can get it – and will continue to get it – is from small number of doctors who are willing to prescribe what we call off-label medicines; medicines that have not been licensed. And if you are a doctor, you are continually being warned by your defence unions and the GMC about the dangers of doing this. Because if something goes wrong, if I prescribed you Rituximab and the next day you collapsed and died, I would be in a terrible mess legally, professionally and probably bankrupt as well, which is why most doctors are cautious or unwilling to go down that route.

Q My GP won’t go down that route. I am interested because I am getting emails from people that have had ME a lot longer than me, and they are getting positive results from it.

Q Could I say something which a doctor will be very well aware of, but I feel a lot of people forget, which is that if you give people treatment – even a purported treatment – if you given them a sugar pill – you will have got a fair proportion, maybe 30 percent of people, who say it worked for them. So that anecdote, as to there being people saying it worked, and YouTube clips of people saying “it worked for me”, the whole point of medical drugs is you are not saying, “It works,” you are comparing people who have essentially a purported treatment to people who have the real treatment, and seeing if there is a difference. That is the thing to really remember, because just having somebody who says it worked for them does not qualify as evidence in the medical sense. Sorry to butt in with that.

A No, no. It is important. Because lots and lots of drugs, like Rifocino, which are used for a totally different purposes – the history of medicine is littered with drugs that have been used for one purpose, then suddenly doctors find that they are useful for another purpose. The other one which we have been talking about is Gabapentin, for pain relief. That is a drug that was used for epilepsy, but it was found that it was also a very effective drug for what we call neuropathic nerve pain.

Q It nearly killed me, that drug.

A What Gabapentin?

A I took it for a year and then I couldn’t see.

Q Right. And yet the anecdotal feedback we have – and it is in our management report, and I know from the experience of people who have used it – that a lot of people with ME/CFS find Gabapentin actually quite helpful.

A We know that one thing for one person is not for another person, which is why it is so difficult.

Q But the only way to take L D N forward is to do a clinical trial on it. Someone has to set up a clinic trial. And the problem with clinical trials these days is that they are very expensive to set up. Unless you have a drug company who is interested in doing it, you are quite often in real difficulties in setting up even a small clinical trial.

Q Drug companies prefer statins,

A They would like everyone on statins. They would like the entire population on statins! (Laughter)

Q You mentioned earlier about coeliacs. What was that, in relation to ME ?

A There is a condition called – a lot of doctors and odd people think coeliac disease just occurs in children, but coeliac disease – which is gluten sensitivity, severe gluten sensitivity – and this is just intolerance. This is really destroying your mucus membranes in the stomach lining. So adult onset coeliac disease, they reckon it has an incidence of about 1 in 250 people. But it can present in different ways. Among the ways that it can present in adults is fatigue, IBS-type symptoms – so a bit of stomach pain, diarrhoea and change in bowel habit – joint pains and it can also have neurological symptoms when it becomes more severe. Of course, as you know, if you go on a gluten-free diet and you effectively treat it, there can be a remarkable degree of recovery. There are people who have adult onset coeliac disease, who have never been tested for it, who get misdiagnosed as having ME – because they have IBS-type symptoms and fatigue – without a coeliac test. And then you get these anecdotal tales from people with ME, “Oh I went on to a gluten-free diet and felt a lot better,” but they were not tested for coeliac. One wonders how many people are out there – there are not that many, but maybe several hundred -- who have got a misdiagnosis of ME, because they have IBS-type symptoms, fatigue, joint pains and whatever, and they are on a gluten-free diet, which has improved their ME. But it is not their ME that has improved, but they have underlying coeliac disease and they have improved their coeliac disease.

Q Am I right in saying that Esther Rantzen’s daughter found out she had coeliac disease?

A I think you are right. It is difficult keeping up to date with what is happening with the family there. (Laughter)

Q You mentioned the check-list of 60 other possible illnesses. Is there no way that NICE have guidelines of doctors, and all the rest of it, shouldn't they be issued with some sort of guidelines, when someone is presenting with possible CFS. Or are you in a position to influence that?

A If you go to the NICE guidelines – it is one of our many criticisms about the NICE guidelines, because I feel they do not go far enough in the business about trying to make sure the diagnosis is correct, and ruling out other things, where it could be, because they do not give sufficient information on some of the rarer things that could actually be going wrong. They talk about coeliac disease and thyroid disease.

Q But they don't check for it

Q When I was first ill, coeliac disease was a very rare illness. But 20 years later it isn't, because they have a new way of looking at it. And instead of being 20,000 people there are about half a million!

A As you say, 20 years ago, when I was doing medicine 20 years ago, very few people talked about adult onset coeliac disease. I am not sure whether the incidence of it has actually increased because of changes in diet and everything else, or whether it is just the fact that it is recognised as a simple blood-screening test you can do for it. The gold test is still a biopsy to confirm it, but more and more people are getting diagnosed about it, because awareness has increased about it and that there is a simple blood screening test for it. So whether it is a real increase in the numbers or not, I do not know; you can only speculate about that. But to go back to your question, in our guidelines for doctors, I go into quite considerable detail about the whole issue of differential diagnosis, and making sure that there is nothing else, with an ME/CFS-like illness that is going on, before you put this label on someone. But it is worrying the way this label does get put far too easily on people, who are going along to the doctors surgery, because they are tired all the time; the doctors run a few bloods tests and they are all negative – and I think part of it is that the doctor just wants the patient off his back. The patient wants a diagnostic label so, “Okay, you've got ME/CFS, which explains your tiredness. Now go away. I can't do anything with ME/CFS. You've got a diagnosis. There you are!”

Q You have contact with the sort of powers that be. Is there no way you can influence them to make this obligatory for doctors to go through this check-list?

A Let me put it this way, that list of routine investigations that I put up, it is fairly similar – ours is a little longer than what is in NICE, and it is fairly similar to what we put in the Chief Medical Officer's Working Group report, which is now ten years old. And it is what is in lots of things that have gone out to doctors. I think any doctor who diagnosed

someone as having ME/CFS without doing at least that very basic list of thyroid, liver, kidney et cetera tests, and diagnosing someone with ME – let us say they didn't bother checking the thyroid – that would be medical negligence if it turned out ---

Q It is already in the guidelines.

A It is in the NICE guidelines.

Q So you don't have to pressure one's GP?

A You shouldn't have to be pressuring a GP or anyone to carry out that very basic list of tests before you get a diagnosis. But it is a very basic, bottom line of tests. If you are working in this area, you will probably add one or two on to that, but that is the absolutely bottom line that everyone should have.

Q Not every GP has read the NICE guidelines, or if they have, they don't remember them.

A No.

Q So you could present them with copies of those relevant pages.

Q Even so, there have been audits of the clinics, and they find that people have been misdiagnosed by GPs – 30 or 40 percent at the clinics do not have the illness!

A The figures for misdiagnosis in some audits that have been done are horrifying.

Q That is why some people who get better have not had ME. It is not a miracle cure?

A This is it! I know most people in this audience have probably got a diagnosis of ME/CFS, but one wonders how many sitting here with this diagnosis have got something else.

Q Every time you get another illness, which they do take seriously, they say, "Oh well you never had ME in the first place." I had cancer – "Oh well, you never had ME." I had diabetes – "Oh well, you never had ME. It was the diabetes."

A Yes. One of the things we recommend in there, certainly once you have got to about 50, is that you probably ought to have some of these routine tests, particularly the thyroid, done every three to five years. Because thyroid deficiency comes on slowly, it becomes increasingly common over the age of 50. It is very easy, over the age of 50, just to say, "Your ME is deteriorating a bit."

Q ME has such a bad reputation with the GPs, that they won't test you for anything!

A I had an email from a patient last week, who pointed this out so vividly, because he wanted us to put a thing up on the website, which we are going to do for him, because he now has type 2 diabetes, and he wants to talk to someone else who has ME and diabetes type 2. But the story was that he felt he was going downhill recently. It seemed to be ME -like. He was more tired, whatever.

Q My results sat on my GP's file for 18 months?

A The GP was on the ball, did the routine tests again – and presumably did his thyroid tests, checked the urine and there it was. His deterioration in his ME symptoms was due to the fact that he was developing diabetes type 2.

TONY: We will have to call it a day. (Applause)