Wetenschap voor Patiënten
(Science to patients)

Seminar 35: Introduction / Experience with ME

Dr. Charles Shepherd. Broadcast 25th February 2014

How did you get involved with ME?

My name is Dr. Charles Shepherd and my involvement with this illness dates back to personal experience, approximately thirty years ago. Like many doctors of my generation when I was in medical school I was told this illness was hysteria. In fact at the time I was at medical school a paper came out in the British medical journal describing ME, Royal Free disease at is was also known at the time as mass hysteria.

So we left medical school believing that we weren't going to see people with this illness and if we did it was all in their minds. And I had personal experience by catching ME from a patient. I actually got a very nasty dose of chicken pox from a patient who had shingles. That changed my mind about this illness. I had all the classic symptoms and yet like many people it took about two years before I got a diagnosis of this illness. During that time I didn't practice the right management, I didn't pace my activity, I had problems with benefits and employment. All the problems that people have to go through with this illness. So my views on ME, especially in relation to management, are very much based on personal experience.

What do you do in relation to ME? (charity, political, research, services etc)

This is very much based on my experience of dealing with vast numbers of people over the past thirty years with this illness. Either seeing them as patients or as dealing with them in my role as medical adviser to the ME Association which is the major adult support charity here in the U.K. So I have a lot of if you like clinical experience in dealing with people on a one to one basis, but I also have a lot of experience in many other areas in relation to my charity roles.

I'm involved in research, I have a particular interest in research relating to muscle abnormalities in this disease. And also the role of vaccinations in triggering this disease. Also within the charity sector we have to provide a lot of information to people with this illness as well as to health professionals. I help to supervise our Ramsay Research Fund which is a major research fund in the U.K. We're currently funding researches such as the ME bio-bank, post-mortem research, and muscle research. And we also have a very important role here in the U.K. in relation to political activity in this illness. We're part of the secretariat of the all-party parliamentary group on ME. And we also play a very important role in campaigning on benefits, which is a particularly important issue for people with this illness.

Wetenschap voor Patiënten
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Seminar 36: What is the difference between ME and CFS?

Dr. Charles Shepherd. Broadcast 25th February 2014

What is ME?

ME stands for Myalgic Encephalomyelitis. And this is a name which came into medical usage following an editorial in the Lancet medical journal in 1956 and it was used to describe an outbreak of this illness that occurred at the Royal Free Hospital in London the previous year. The outbreak at that time was being called the Royal Free disease but the Lancet editorial named it myalgic encephalomyelitis. And it was the term that was used because these patients had muscle symptoms, which is where the 'myalgic' comes from, and they also had a lot of brain symptoms which is where 'encephalomyelitis' comes from. And in medical jargon encephalomyelitis means inflammation which is 'itis', within the brain which is 'encephalo', and 'mya' which means spinal cord. It means in pathological terms inflammation within the brain and spinal cord.

What is CFS?

Chronic fatigue syndrome is a name that was introduced by the medical profession during the nineteen eighties. Partly as a reaction to the fact that there was renewed medical and scientific interest in this disease, and partly because the medical profession decided that it did not like the term ME myalgic encephalomyelitis, because there has always been and there continues to be a considerable degree of controversy and uncertainty as to whether there is actually inflammation within the brain and the spinal cord.

So the medical profession in its wisdom decided to rename and redefine ME as chronic fatigue syndrome. And the way it redefined ME as chronic fatigue syndrome, is that it brought in a lot more people under this umbrella of chronic fatigue syndrome who previously would not have met the diagnostic criteria for ME.

A lot of patients of course dislike the term 'chronic fatigue syndrome', I dislike the term chronic fatigue syndrome, because I feel we've widened the diagnostic net as to who comes under this umbrella of chronic fatigue syndrome. And in a way it's rather like saying that everyone who has some form of headache whether it's a migraine headache or even a brain tumor headache can be put under an umbrella of a chronic headache syndrome. And so they all have the same cause and they all have the same form of management. Which clearly isn't the case.

What does the combination ME and CFS stand for?

The combination-term of ME/CFS is really a messy compromise to try and keep the medical profession on side, who certainly in the UK, and I think this will be true for the USA and

many parts of Europe where this illness is recognized; to keep the medical profession on board who wants to use the term CFS, and the patients who not surprisingly-and I agree with them-want to use the term ME. So we have this messy compromise of ME/CFS. And in actual fact I think what we have also is an umbrella which is covering a wide variety of clinical presentations. And equally it's covering a wide variety of disease pathways or subgroups. So it's going back to this headache syndrome or joint pain syndrome.

We're trying to put everyone who has some sort of chronic fatigue under this ME/CFS umbrella. And I think we're very wrongly saying that they probably all got the same cause, so that they all got the same form of treatment. And what I think we've got to do, which is I think what the research community is now taking on board, is to go back several steps and try and subgroup these people who come under this ME/CFS umbrella into clinical subgroups, pathological subgroups. So that we can find effective treatments for these different subgroups under this umbrella, because quite clearly not everyone under this umbrella is going to respond in the same way.

Why do most doctors prefer CFS to ME?

I think the vast majority of my medical colleagues remain convinced that ME is not an appropriate name for this illness, largely because this problem with encephalomyelitis and the lack of pathological proof or evidence that there is an inflammation taking place within the brain and spinal cord. There are certainly abnormalities taking place within the brain, and we know that from research. But we don't have any hard scientific evidence to demonstrate inflammation in the brain and within the spinal cord.

What would you call the disease?

My way round this is to propose that we actually rename Myalgic Encephalomyelitis Myalgic Encephalopathy, which would take the inflammation out of the encephalomyelitis and imply that we have an illness here which is affecting muscle and brain function which is what encephalopathy is but without the widespread inflammation. So I have proposed that to some of my colleagues. It is something which is accepted here by the government, the department of Health, NICE but it hasn't yet achieved any sort of degree of widespread acceptance. So at the moment we remain in this very unsatisfactory position where we have patients calling the illness ME, and doctors calling it CFS. And those who want to try to make some sort of compromise are calling it ME/CFS.

My preference is to use the term ME as myalgic encephalopathy which takes the heat out of the argument and I find when I use this in the presence of my medical colleagues it is accepted normally without any great problem. But if I go and talk to my medical colleagues about myalgic encephalomyelitis, instead of actually talking about the illness, talking about how to diagnose it, talking about how to manage it, it just stems back into an argument about the fact that there is no encephalomyelitis. And I think as long as my medical colleagues remain so unconvinced and even hostile to the concept of encephalomyelitis I think we have a major problem. Because all that results in is my colleagues abandoning the term ME and using what I regard as this awful term 'Chronic Fatigue Syndrome'.

Wetenschap voor Patiënten
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Chat: questions and answers

On Friday 28 February 2014 dr. Charles Shepherd answered questions in a chatwing-session. These are the Q&A of this session.

Q: You are saying that it is uncertain as to whether there is an actual inflammation within the brain and the spinal cord. I think most (99,9 %) of the patients didn't get any testing for that. So how can you say there is no inflammation of the brain? I myself feel it every day.
A: I am one of the few doctors who is involved in post-mortem research, and the results from a small number of these post-mortems have been published. The bottom line here is that encephalitis (widespread inflammation in the brain) has not yet been found in these PMs. Neither has widespread inflammation in the spinal cord been found.
What we have found is dorsal root ganglionitis - inflammation of tiny nervous structures that lie just outside the spinal cord in the peripheral nervous system and are responsible for processing sensory information like pain and touch.

Q: It can't be found on scans?
A: You can make a diagnosis of an acute encephalomyelitis through a combination of clinical history, examination findings and abnormalities on neurological investigations, including scans. But you do not see this combination in people with ME/CFS.

Q: You are saying in your video using ‘opathy’ takes the "heat" out the situation - of course it does, for it still leaves the diagnosis wide open to how you want to choose to interpret it : mental or physical. Because the word ‘opathy’ , exactly like CFS, has a dual interpretation : it can be interpreted physically and/or psychiatrically. So how do you make clear which one is which?
A: I obviously have considerable sympathy with people who believe this illness should be called M encephalomyelitis as my own illness was triggered by a chickenpox encephalitis. But in our current state of knowledge I do not believe that M. encephalomyelitis is a correct way of describing the pathology. This is why I have advocated the use of the term M. encephalopathy - as this is consistent with the abnormalities that have been published

Q: How can the large differences between patients be explained? Why are some patients bedridden, while others still are able to work and have some social life?
A: Nobody has a satisfactory answer as to why some people with ME/CFS improve, others remain more static and variable, whereas others become severely affected. Partly because so little research has been done on people with severe ME/CFS.
The MEA has funded research into factors that may be involved in severe ME/CFS and the ME (blood sample) Biobank at UCL in London that we are funding is collecting blood samples from people with severe ME/CFS to see if there are any characteristic differences in severe cases.

Q: You said you catched ME from a patient. Is ME contagious?
A: I caught chickenpox virus from a patient of mine who had shingles (same virus). The CP virus then triggered my ME. It is the triggering infection that can be spread to other people. There is no evidence that ME/CFS can be passed from person to person.

Q: So you mean that ME is the outcome of a disease instead of a disease itself. It can have numerous causes?
A: A large number of viral infections, including hepatitis, can trigger ME/CFS. It can also be occasionally triggered by non viral infections (e.g. salmonella) and other types of immune system stressors such as vaccinations. I have a large collection of people with ME/CFS who predate the onset to a vaccination - health workers following hepatitis B vaccine in particular.

Q: And is the trigger that causes the ME responsible if you get mild or severe ME?
A: Think of ME/CFS as a three stage process involving 3Ps. Genetic factors that Predispose to its development. Immune system stressors (e.g. infections) that Precipitate the illness, And a complex range of resulting abnormalities involving brain, immune system, endocrine system that Perpetuate the illness.

Q: Are there perspectives in the development of a medicine or are the researchers groping entirely in the dark where the disease is lodged in the body?
A: ME/CFS is perpetuated by a complex interaction between abnormalities involving brain, muscle, endocrine/hormone system and immune systems. Until we understand more about these abnormalities and how they interact it is going to be difficult to find a drug treatment that deals with the underlying disease process.
One promising lead which you may have heard about is a drug called Rituximab. This is normally used to treat people with lymphoma - a type of cancer. But some Norwegian doctors have found that it appears to benefit a subgroup of people with ME/CFS. The reason for this may be due to the fact that Rituximab dampens down a part of the immune system that produces autoantibodies - harmful antibodies that can attack/damage healthy tissues and organs.

Q: Are you cured from ME or are you coping? And what is your secret?
A: I am not 'cured' of this illness. Like many people I see I have made a degree of recovery but have now hit a 'glass ceiling' whereby I function at around 60% to 70% of my normal healthy self - with occasional ups and downs, often triggered by an infection.
I don't have any secret solution. I don't take any drugs or supplements. The main factor in achieving a degree of recovery has been learning how to correctly pace my mental and physical activity and (I know it's not easy) staying positive. Also having good support from family and friends

Q: What do you think of the use of valganciclovir?
A: There are certainly some interesting results from small clinical trials involving valganciclovir and I have been over to America and met one of the doctors using valganciclovir. I have also had a meeting here in the UK with the drug company involved to try and persuade them to set up a clinical trial - but no luck so far.
What we need are some larger clinical trials carried out by other clinicians to see if this drug might be a safe and effective option for a subgroup of people with ME/CFS, possibly those

who have evidence of reactivation of HHV-6 infection coupled with 'infective' type symptoms.

Q: Yes I have heard of it, but it can be dangerous too. Is it possible to try it ? And how do I get it if it is possible?
A: Here in the UK doctors would be very reluctant to prescribe an antiviral drug like valganciclovir - unless there was a very good reason for doing so. This is because these drugs can have quite serious side-effects. I suspect that a similar situation exists in other parts of Europe.

Q: Is there any treatment with medication you would advise ?
A: In our current state of knowledge I am reluctant to either use or recommend what are best described as speculative forms of drug treatment. Drug treatments do, however, have an important role in helping to relieve symptoms such as pain, sleep disturbance and irritable bowel type symptoms - as well as depression if it occurs.

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Seminar 37: How is ME diagnosed?

Dr. Charles Shepherd. Broadcast 11th March 2014

What diagnostic criteria are used?

There are a number of diagnostic criteria for both ME and chronic fatigue syndrome. For ME we have doctor Melvin Ramsay's original description of the illness. We have some criteria called the London criteria, we have International criteria, newly prepared criteria for ME. For CFS we have a range of criteria today. We have Fukuda criteria, we have Australian criteria, we have Oxford criteria here in the UK and we also have NICE criteria in the UK. And for both ME and CFS these criteria have similarities and differences and even within the criteria for ME and CFS there are similarities and differences. So this is a picture of great confusion for the average general physician who is presented with a patient in his consulting group who just wants to make a simple straightforward diagnosis of this illness. So I think most of my colleagues, just like the approach I would take, take a pragmatic view to diagnosing this illness. And we make use of these criteria which I have to say primarily are there for research purposes to identify people going into research rather than clinical purposes. So we make use of these criteria but we don't stick to them rigidly when we make a diagnosis of this illness.

To make a diagnosis of ME or CFS or ME/CFS it is the same process that you go through when you're making a diagnosis of any illness. You take a history, you examine the patient, you arrange some blood tests which we will come to shortly. As far as the initial part of the clinical consultation is concerned, it is extremely important to take a detailed history from patients with a possible diagnosis of ME. Because there are many other illnesses which can overlap with this illness and cause diagnostic confusion. So the history taking is extremely important and if there are other symptoms there in the history which are not typical of ME, they need to be pursued to make sure that you're not missing some other diagnosis. It's terribly important to examine the patients carefully, particularly their nervous system and muscle although on the whole you're not going to find any particular diagnostic examination abnormalities which are characteristic of this illness. You may find problems with balance, you may find problems with muscle weakness, you may find abnormalities in some parts of the nervous system examination but on the whole, examination doesn't add an awful lot to the diagnosis of this illness.

Which tests should be arranged when a diagnosis is considered?

When you're considering a diagnosis of ME, it's terribly important to check through a quite comprehensive range of blood tests and some urine tests. These tests are done not to diagnose ME, because we don't have a diagnostic blood test for ME, but they are there to make sure that you're not missing other conditions. So you want to check thyroid function,

you want to check liver function, kidney function, routine hematological checks, checks of inflammation or infection in the body, a very sort of wide-ranging test is what's called the ESR. And this list of tests is available, readily available, in all the sort of guidelines that are issued to doctors who are making a diagnosis of ME. They're comprehensively described in the MEA booklets on diagnosis. So those are tests which have to come back as normal before you should be making a diagnosis of ME.

Now there are also a range of what we will call second line tests, which range from brain scans to immune function tests on the blood, something like even muscle biopsies. Now you cannot arrange to do every single one of these tests in every patient who comes along for this possible diagnosis. It's not feasible, it's not workable, it's just not costable. So with these second line tests you have to reserve which ones you're going to do on the basis of clinical judgment. This will be based on whether or not there are symptoms which we might describe as red flag symptoms. So you got a patient who is losing weight, well that would immediately suggests that you need to be looking to do further investigations before making a diagnosis of ME. Or they have unusual symptoms, perhaps they have skin itch, skin irritation suggesting that they have a condition called primary biliary cirrhosis that can overlap with ME. Or they may have dry eyes, dry mouth, joint pains, suggesting they may have Sjogren's syndrome, in which you would want to go often do specific immunological tests, anti-auto antibody tests. They may have symptoms which are overlapping with multiple sclerosis, which can occur. And sometimes it is quite difficult to differentiate between ME and MS. And in that case you want to go off and do brain scans or whatever to look for a possible diagnosis for ME. So there are a lot of different tests which may be applicable but in certain circumstances. And using your clinical judgment as a doctor that's the situation when you go often do that sort of tests.

What other conditions should be considered before a diagnosis is confirmed?

Before a diagnosis of this illness is confirmed, as I was saying when we were talking about taking a very careful clinical history from patients, it is important to have at the back of your mind as a doctor that there are a large number of conditions - we list about fifty different conditions in the MEA booklet on this – that can be misdiagnosed as ME because the symptoms overlap. So when you're going through this history, you need to be aware and pick out symptoms which are not quite consistent with the diagnosis of ME and then start querying could that be another condition.

Let's take a couple of examples. You have a patient who comes along who has their fatigue, but also has a lot of bowel problems as well. Irritable bowel typed symptomatology. Now we know that irritable bowel typed symptomatology, bloating, alternating constipation and diarrhea, stomach pains is quite a common accompaniment to ME. A lot of patients with ME do have this. And it is quite tempting to just say well you got ME and you've got a bit irritable bowel syndrome. But when you have a patient like that who comes along what should be going through your mind as a doctor is, could this patient also have something like adult onset celiac disease? Which is not uncommon in the adult population, which is treatable to a large degree and can be misdiagnosed as ME. So you get a patient with fatigue, irritable bowel typed symptoms you should be doing a screening tests to rule out celiac disease at the same time. Another example might be, you get a patient with fatigue and joint pain. And we have a condition called joint hypermobility syndrome which can overlap with ME. And again there would be a different form of management if you had someone with joint hypermobility syndrome. Interesting about joint hypermobility

syndrome is that these patients often have bruising as well. So that will be another warning sign there. So there's a lot of different conditions which need to be seriously considered before you come to this diagnosis and say you've definitely got ME.

Who can make a diagnosis?

The diagnosis of ME in most cases, I stress most cases, is something that should be capable of being made by a good general practitioner, that's a doctor in primary care. Where a doctor in primary care is unable to make a diagnosis, then there should be facilities available at the local hospital. Either through an ME/CFS clinic or a specialist at the local hospital who has widespread experience in dealing with this illness, to whom a patient should be able to be referred for a confirmation of the diagnosis.

What about the International Consensus Criteria?

The International Criteria is the latest and most comprehensive criteria which aim is to be able to help doctors make a diagnosis of ME. It is a very detailed criteria and, as I've indicated earlier, I think most of my medical colleagues take a very pragmatic approach to making a diagnosis of this illness, and don't tend to sit there with a diagnostic criteria especially if it is long and complicated, sitting on their consulting room table. So I think as an aid to diagnosis this is a very helpful document. But I think to expect that every doctor is going to sit there with this criteria in his waiting room, consulting room and then using it to make a diagnosis of ME is probably unrealistic at this point.

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On Friday 14 March 2014 dr. Charles Shepherd answered questions in a chatwing-session. These are the Q&A of this session.

Q: I'd really like to know how Dr. Shepherd is at the moment in terms of his own ME - and what helped him!
A: Like many people with ME I have hit a 'glass ceiling' where I function at about 60% to 70% of what I regard as 'normal self' for most of the time. Having tried a wide range of drug treatments over the years I'm sorry to report that I didn't personally find any of them to be effective.

Q: That is my experience too. But what about the key question of whether to exercise, rest, or do some smart combination of both?
A: The one thing that has been of more help to me than anything else has been learning to properly pace my mental and physical activities. Trouble is, this has to be done through a combination of personal trial and error and help from a health professional who knows about ME/CFS (and is not easy to find!)

Q: Have you ever been bedridden? or at least couch?
A: My illness started with a chickenpox encephalitis -- which I contracted from one of my patients with shingles - so I did have a period of severe illness (in bed) early on. But apart from occasional relapses, normally triggered by an infection, I am now vertical and mobile for most of the day.

Q: Did you resent him/her for it? ;) and scary occupation you have...
A: Doctors do sometimes pick up nasty infections from their patients - that's life!

Q: Dr. Shepherd, in the interview you state that there are no confirmative tests for ME. Others maintain that they have such tests (e.g. Sarah Myhill and Kenny DeMeirleir). Why, do you think, is there such a difference of opinion among experts?
A: I wish we had a biomarker or test (blood, neuroimaging etc) that could confirm that someone has ME/CFS but that is just not the case at present. I know that some of my colleagues believe that they have such tests - but this view is not shared by the majority of docs working in this area.

Q: What about De Meirleirs H2S-test?
A: I have to say that I am not yet convinced by the validity of the H2S test in relation to ME/CFS. It is not used here in the UK.

Q: In your talk of 25 February (36), you proposed a new name instead of ME or CFS: myalgic encephalopathy, in order to reduce the confusion about the name. But, given the fact there is a lot of research, would it not be wise to wait with a new name until the "final" cause(s) of this illness have been found? A third name can even increase the confusion.

A: I proposed a new name - myalgic encephalopathy - at a time when there was tremendous pressure on the medical establishment to get rid of M encephalomyelitis here in the UK, where many doctors just will not use the term ME because they do not believe it reflects the pathology.

Q: If you compare the results of the different researches to ME/CCVS, in what direction do you suppose the cause and treatment of this illness will be found?
A: My best guess is that we are going to find the answers through a better understanding of what is going wrong in the brain and nervous system. This is because ME involves a combination of central (i.e. brain) and peripheral (i.e. muscle) fatigue and as central fatigue is a dominant feature in a number of other neuro illnesses (e.g. MS, Parkinson's) I think we are going to find some interesting answers through collaboration with other neurodiseases.

Q: Do you still support the name myalgic encephalopathy, or are you now convinced that ME involves CNS inflammation?
A: I still support and use the term M encephalopathy in preference to M encephalomyelitis. Whilst I do not believe that ME involves widespread inflammation in the brain and spinal cord I do believe that neuroinflammation plays a role - and this is one of the MRC research priorities here in the UK. I am one of the few docs involved in post-mortem research and our group have published preliminary results supporting a role for neuroinflammation in ME/CFS- i.e. the presence of dorsal root ganglionitis in some cases. If you remind me on MEA Facebook later I will give you the reference.

Q: In terms of neuro research are we going to find damage or an ongoing infection do you think?
A: In relation to neuro research I would be surprised if we find evidence of on-going infection or significant structural damage. If this was the case I think it would have been shown by now. What is encouraging is that new forms of neuroimaging mean that we can learn much more about brain activity, blood flow etc
And along with info on brain chemical transmitter activity this means that we could get a better understanding of the underlying disease process and effective forms of treatment

Q: Proof of Post Exertional Malaise, PEM, seems to me to be the single most important thing we can achieve to validate ME, practically for patients & also prevent harm from draconian exercise therapies.
A: PEM is a cardinal clinical feature of of ME/CFS and it is surprising that it has not been more thoroughly researched. The MEA is funding Prof Jo Nijs (Belgium) and Dr Lorna Paul (Glasgow) to carry out a study that will be looking at the role of immunological and neuroendocrine factors in the causation of PEM.

Q: Do you think the latest findings regarding the role of latent EBV (Loebel et alea) will help explain the pathogenesis of ME?
A: I suspect that findings relating to reactivation of EBV and HHV-6 viruses are going to be markers of underlying immune dysfunction. You may have seen that the UK ME Biobank, which the MEA funds, has been given a $1.5 million grant from NIH to carry out a three year study to look at this aspect.

Q: Dr Shepherd do you agree with the majority of British doctors, NICE etc and see your ME as a pyschiatric or psychological condition?
A: I would say that most UK doctors view ME or ME/CFS a a combination of physical and psychological. A minority view it as purely physical and another minority view it as purely psychological. A small number still do not believe that it exists as a clinical entity.

Q: Does current VO2 exercise testing contain too much of a subjective component atm to be accepted as a biomarker? Because otherwise, it would *really* help folk to be able to demonstrate that ME isn't 'all in the mind' (as was again put forward, w/o evidence, in Spectator today). Sorry, answer other questions first.
A: I went to a lecture given by Prof Van Ness a few weeks ago and my view is that the VO2 test is a potentially very interesting and useful finding - but it does need replicating by other independent research groups. We also need results from people who are deconditioned or have a degree of cardia-respiratory failure.

Q: I don't know about anyone else here but I've still to meet an NHS GP who gives me any clear indication that they believe my experience has any pathology in the body, they have ways of indicating that
A: Yes, it does. Are you aware of the MEA Guidelines booklet I produce reach year - 52 pages of fully referenced (over 300 key references) info on diagnosis, tests, management and key research findings. We can send a free copy to your GP - see MEA website or Facebook for how to do this.

Q: "Replicating by other independent research groups" - Can the MEA do this?
A: Yes, a vital part of the research process is replicating other people'e research. This is why we need further trials into Rituximab. The MEA Ramsay Research Fund is happy to consider such proposals and we would certainly be interested in one relating to the VO2 exercise testing.

Q: What is your opinion about cognitive behaviour therapy and get? Is it possibly helpfull, not helpfull or even destructive?
A: The form of activity management that I advocate is pacing - the problem with GET is that it is too inflexible and fails to take account of stage and severity of the illness. In patient UK surveys around 50% of people report being made worse by GET.

Q: What is your opinion of something like the Lightening Process?
A: I have been very critical of the Lightning Process and have reported a number of LP practitioners to the regulatory authorities here in the UK. The MEA position on LP is summarised in the Alternative and Complementary treatment section on the MEA website.

Q: Have had ME for 15 years and have been on calcium channel blocker for increased breathlessness for some years. Syndrome x has been mentioned - is this seen often with or even associated with ME. Currently seeing immunologist at Newcastle and clinic for M.
A: Yes, syndrome X has been associated with ME/CFS. As you are in the UK I suggest you order a copy of the MEA purple booklet - where it is discussed in the research section.

Q: Also low dose naltrexone (LDN) has gained a little popularity. I've found it great for my strange neurological morons such as muscle solidness, spasm, twitches, involuntary leg jerks… yet there seems to be little awareness about it. Also gave me incremental improvements in functioning. I just thought I'd make it known, that depending on your symptoms, there could well be an existing medication that's good for ME, as well ad other conditions. But typically it's on private prescriptions.
A: There is quite a lot of anecdotal support for naltrexone here in the UK but some people also report that it has made them worse, In the absence of results from a proper clinical trial this is not a drug that I would use or recommend in our current state of knowledge.

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Seminar 38: ME and its triggers

Dr. Charles Shepherd. Broadcast 25th March 2014

What role do infections play in ME?

Infections play a very important role in this illness. I think it's probably helpful just to recap on how this illness probably develops. And I think there are three stages to this illness: there are things that predispose towards this illness, particular genetic factors, there are things that precipitated or trigger it and then there are things that perpetuate it or keep it going. The role of infection comes into the second stage, things that perpetuate things that precipitate or trigger this illness. And we know that in round about 75% of cases people will predate the onset of their ME to a very clear cut infective episode. They will describe an infection. It may be something quite straightforward like a flu-like illness or a respiratory tract infection, gut infection. It may be a rather more specific infection like glandular fever or chicken pox. And they will say "I got that infection and I never recovered from that infection".

We know as I say that there are a number of viral infections, particularly viral infections, that seemed to do this. But at the same time there also a number of cases where non-viral infections seem to trigger ME. We know that Q fever can cause an ME like illness. We know that some people develop ME from salmonella infections, although these are rare. It is primarily viral infections that seemed to trigger ME. So that is somewhere where we have a great deal of certainly. Where things become rather more complicated and uncertain and the research evidence is somewhat conflicting, is whether these infections that actually trigger ME then go on to persist in the body and play a role in keeping the illness going. In other words do persisting viral infections also play a role. And as I say the evidence here is somewhat conflicting.

The other aspect to infections is that part of the perpetuation of this illness seems to be involving the role of the immune system. On a way that the immune system triggers and kicks in once you have the precipitating viral infection. Part of the immune system disturbance in ME may involve what we've call reactivation of latent viral infections. So these are infections that you already had hanging around in the body that particularly herpes virus infections like Epstein Barr virus and human herpes virus type 6. And there is certainly some evidence from the research studies that are being carried out, that once the viral infection has taken place, the immune response has taken place, that some of these latent viral infections then become as it were reactivated more active again. So it could well be that the viral infection that triggers this illness off, is not playing any further role in keeping the illness going. But as part of the immune system response to that viral infection there is reactivation of latent viral infections within the body. So it's quite a complicated picture.

And of course this is something that really does need to get resolved because there are quite powerful anti-viral drugs which can help as a possible form of treatment for this illness, if viral infections are involved in keeping it going. All these reactivated viral infections are involved. And one such drug is called valganciclovir and there have been some small clinical trials taking place. Another one was recently reported from Jose Montoya's group in Stanford in California suggesting that there may be benefit from giving an anti-viral drug, particularly if you get the right subgroup of patients with the reactivated viral infection, you give them a course of valganciclovir, valcyte. So that is an interesting approach to the role of infection in this illness.

Are there other possible triggers for ME?

I think there are other things that trigger this illness of in addition to the viral infections that we've already been talking about. These are things that we would term immune system stressors. And I have a particular interest in the role of one particular immune system stressor which is a vaccination. Which is essentially mimicking the effect on the body's immune system of an infection. And we know that a small but significant number of people with this illness will either predate the onset of their illness to a vaccination, although they describe a very significant exacerbation of symptoms, or a relapse following a vaccination. It's quite interesting when you look at reports from people who describe the onset of their ME following a vaccination, that there is certain vaccinations which seem to be heavily weighted in this respect. One vaccine in particular is Hepatitis B vaccine which seems to be a trigger factor for this illness. Quite a considerable number of people that I've collected over the years. So whether there is something slightly strange about Hepatitis B vaccination in relation to ME, we're not quite sure at the moment, but it certainly has been linked to the onset development of other autoimmune disorders such as SLE in the medical literature.

Having said all that I think it's important also note that in addition to all 75 % of people who predate the onset to a fairly clear cut infection or perhaps a vaccination, we have a group of a significant minority who develop this illness in a rather more gradual fashion and do not predate the onset of their illness to any particular event whether it's infection, vaccination or whatever. They may describe a series of infections after which they become more and more unwell and eventually if you like slip into a ME/cfs like illness. But they don't have a clear cut factor which seems to be triggering their illness.

Can a trauma be a trigger?

Trauma can occasionally be a trigger factor in the development of this illness. And just like infections and vaccinations it can sometimes cause a major relapse or exacerbation of pre-existing symptoms. So we do have a small number of people who will predate the onset of their illness to perhaps a major road traffic accident. Another form of physical stress if you like which sometimes is described as an onset to this illness is in people who undergo major surgery general anesthetics. So I think you could bring those people into this group as well.

Wetenschap voor Patiënten
(Science to patients)

On Friday 28 March 2014 dr. Charles Shepherd answered questions in a chatwing-session. These are the Q&A of this session.

Q: My ME/cfs was probably triggered 13 years ago due to being pregnant. After 1 1/2 year I felt better, but always very tired. It never went away. Inflammations. Is this also known as a trigger for ME? What do hormones have to do with it? Now that I am 44 years old, there is a new inflammation of ME since 1 year. Do hormones maybe play a role again?
A: A number of what we call immune system stressors can trigger ME/CFS - one of which is pregnancy. The explanation probably involves a combination of immune system and hormonal changes that occur in pregnancy. Also interesting to note that a significant number of women with ME improve when pregnant.
There is also some research information (paper in The Lancet from gynaecologists Studd and Panay) to indicate that changes in female hormone patterns can affect ME/cfs symptoms. It's referenced in the MEA purple booklet: Studd J and Panay N. Chronic Fatigue Syndrome. Lancet, 1996, 348, 1348.

Q: How do pregnancies usually progress for women with ME/CFS? How common is it that there is an improvement? And does this improvement last after the pregnancy? And are there risks?
A: Most (but not all) women notice an improvement (sometimes quite significant) during pregnancy. Unfortunately, many then return to their normal state of ME/CFS once the baby is delivered and life gets more physically and mentally demanding! Are you involved in getting pregnant when having ME/CFS? A good review of what happens to women with ME/CFS during pregnancy you'll find in this paper - Schacterle RS and Komaroff AL. Archives of Internal Medicine, 2004, 164, 401 - 404.

Q: In your college you mention several possible causes of ME of CVS. What do you think of the role of ongoing stress? Can it be a cause of ME/cvs?
A: To clarify: I am saying that there are a number of factors that involve a stress on the immune system response which appear to be involved in triggering ME/CFS. Infections (viral more than bacterial) are the most common - but other triggers include vaccinations, trauma, operations, pregnancy and pesticide exposure. Mental and/or physical stress can be an important factor in both helping to trigger ME/CFS when, say, you have an infection. On-going stress can also be an important factor in preventing or delaying any natural recovery process that may be taking place. And this is why stress management (through relaxation, meditation etc) is an important part of management if/where stress is playing a role in maintaining the illness.

Q: In your college you mention a large number of possible causes. How is it possible that so many various illnesses all can cause the same illness ME in the end?
A: There isn't a single underlying problem in ME/cfs. The illness is maintained by a complex interaction involving a number of brain abnormalities plus abnormalities in the immune system, hormones and a biochemical deficit in the way the muscles produce energy.

Q: Do I understand well that physical stress has the same impact on the brain as other stress, such as fright?
A: There are similarities and differences as to how the body responds to physical and mental stress. With mental stress part of the nervous system called the autonomic nervous system goes into overdrive with the production of chemicals (e.g. adrenaline) that produce symptoms such as raising the pulse rate and sweating.

Q: Is it possible that the hormonal changes during the menopause cause less bowel problems due to ME/CFS, such as chronic diarrhea?
A: I don't think you can easily link hormonal changes during the menopause to the very common irritable bowel type symptoms that occur in ME/CFS. This is more likely to be due to a disturbance in a part of the autonomic nervous system that controls the emptying activity in the bowels. Changes in a chemical transmitter called serotonin may also be involved in the irritable bowel type symptoms that often occur in ME/CFS

Q: Do the hormonal changes during the menopause commonly cause no changes in ME/CFS symptoms?
A: Hormonal changes that take place during the menopause can cause a number of symptoms that also occur in ME/CFS (e.g. sweating, fatigue, problems with memory and concentration) So it is quite common to find that women going through the menopause report an exacerbation of their ME/CFS as well.

Q: What is the SMILE-trial actually about?
A: The SMILE trial is a UK trial that has been looking at the feasibility of using the controversial Lightning Process as a form of treatment for young people with ME/CFS. The MEA opposed the trial for a number of reasons and argued that if a trial was going to take place it should involve adults, not children.

Q: Is the main question: where do the abnormalities start, in the brain or peripheral?
A: I think the sequence of events is that a triggering infection causes an abnormal immune response (possibly involving over-production of chemicals called cytokines) which then affects various parts of the brain and the brain-hormone systems (especially hypothalamus and cortisol production).

Wetenschap voor Patiënten
(Science to patients)

Seminar 39: ME, exercise and the mitochondria

Dr. Charles Shepherd. Broadcast 7th April 2014

What are the effects of exercise on someone with ME?

The effect of exercise on people with this illness is very characteristic and it is really a diagnostic key, a diagnostic feature of the illness. So that when people exercise their muscles run out of energy, they run out of the capacity to perform exercise. So what we term exercise induced muscle fatigue is, I believe, what is probably the hallmark of this illness. Interestingly enough, when people exercise beyond their limitations they will also get what we call post exertion malaise, post exertion fatigue. This can sometimes be delayed for several hours or even 24 hours. So they go to the point to their exercise tolerance and stop, but the following day perhaps, they then feel that they've got an exacerbation of their symptoms because of this symptom of post exertion malaise.

What is exercise tolerance time?

Exercise tolerance is a term that we would normally apply to exactly how long someone can exercise for before fatigue sets in, quite often pain sets in and then if they continue after that actual weakness and unsteadiness of the muscles will occur. It's a very variable factor with people with ME. So someone at the mild end of the spectrum with this illness they may be able to go for a walk for half a mile, perhaps even longer before they're starting to feel fatigue and weakness. Whereas someone who is more moderately affected may only be able to walk perhaps a hundred or two hundred yards. An absolute maximum before they reach the point at which they cannot carry on any further. And of course people at the severe end of the spectrum, who are wheelchair bound, bed bound and house bound, they would have very very limited tolerance for any form of physical activity or exercise.

The other, I suppose, characteristic of this is it depends what sort of exercise activities are being undertaken. If it's a short burst of terribly strenuous or physical activities like saying trying to go for a ride on a bike or a run or something which someone with ME would not be able to do, but if you put someone with ME through that sort of exercise their ability to sustain that form of high-intensity exercise will be very very short. Whereas if it's low-intensity exercise, walking for instance as I say, there would be a wide variation in the tolerability as to how far someone would be able to do that.

What is the effect of ME on the muscles?

The effect of ME on the muscles is this symptom which I already described of exercise induced muscle fatigue. So we have this range of muscle symptoms which develop progressively after someone has been doing any form of activity. So fatigue will set in in the

muscle, pain will probably set in in the muscle - but not always – and then if the activity is pushed on beyond the persons limitations, actual weakness will occur in the muscles.

How can one avoid exerting oneself too much?

To avoid getting these muscle symptoms and overexertion, to a certain extent it requires a process of trial and error. It's something that people with this illness learn to develop and the way which we try to make people understand the best way to cope with this key symptom of ME is through a process what we call pacing. This involves very careful management of activity and rest or relaxation.

So what we would advise patients with this illness to do is to pace their activities. So that they are not exceeding their limitations, they are dividing their physical and their mental activities into little small chunks, so they do a little bit of physical activity within their limitations. They then have a period of rest or relaxation. Perhaps after a bit of physical activity they might do a bit of mental activity, and then they have a period of rest or relaxation.

What is important not to do is, and this takes people into what we call a boom and bust cycle, is to push on to the point of physical exhaustion, fatigue and then stop because then you're just going to get a prolonged period when you'll not be able to do anything and return to activity. So it is very important to try and pace activities, with little bits of activity, gaps in between, followed by little bits of activity.

What's the difference between pacing and GET?

The difference between pacing and graded exercise therapy very much depends on who is recommending the particular form of treatment. But in very simple terms pacing is living within your limitations. But at the same point within those limitations, given the fact that you are having little gaps, little periods of rest or relaxation between activities, gradually trying to increase the amount of time you are spending on a physical or mental activity. But certainly not pushing yourself beyond your fatigue barrier.

Graded exercise is a rather more structured and pro-active form of activity management in which people are, if you like, often encouraged to push beyond their boundaries and not necessarily take a rest when you would be taking a rest during pacing. Our experience, certainly in patients surveys, is that 90 % of people who respond to patient surveys on activity management find that pacing is a very effective form of activity management. Very few people report any sort of adverse effects to it. Whereas if you look at patient opinion on graded exercise you will find that up to about 50% of people in these surveys report graded exercise actually makes them worse. But there is a small number of people who find graded exercise to be helpful in their management.

I suspect this reflects the fact, going back to my previous points about this big umbrella of people that come under this term chronic fatigue syndrome, that there are people who have an illness of one end of the spectrum which may well be more of a psychiatric type of illness who respond to this type of approach. Opposed to the people at the other end of the spectrum with very much a physical ME type illness, who are much more likely respond to pacing.

How to deal with relapses while pacing?

The way to deal with relapses in relation to pacing is first of all to try and make sure that you can recognize as soon as possible that you've got an exacerbation of symptoms going on or that your illness is going into a relapse phase. To a certain extent this is fairly recognizable because most of the things that we know cause ME are also the sort of things that tend to cause a relapse. So relapses are in particular caused by infections, sometimes they can be caused by vaccinations, stress seems to play a particularly important role in causing relapses and sometimes a physical trauma. We talk about road accidents, we talk about surgical operations could cause a relapse. So if you are aware that any factors are going on, like an infection, that is likely the cause of a relapse, you need to modify your pacing program to take that into account.

So you would drop the degree of activity you were doing, both physical and mental within those little chunks, to a lower level. You would decrease the time you were doing involved in those activities and you would at the same time extend the period of rest and relaxation between your activities. So it's a very careful balance that has to be struck, and again as we are learning how to do pacing, it's very often a question of trial and error before you actually pick up and learn how to do it properly.

What role do the mitochondria play in ME?

The mitochondria play a very important role in ME. Mitochondria are tiny little, what we call organelles within the muscle and they're rather like Duracell batteries within the muscle. They're the places where chemical reactions take place which break down sugars, which were taken from our diet to actually form energy in the form of something called ATP. We know from our work. Actually the very initial stuff on mitochondrial dysfunction in this illness was done on some of my own skeletal muscle, this was done over thirty years ago, and the results were published in the Lancet. We demonstrated with someone called professor George Radda from Oxford the fact that when I exercised there was an abnormal increased amount lactic acid being produced in the muscle. Which is indicative of a problem within the mitochondria.

At the same time some research was being done by a colleague of mine, professor Peter Behan up in Glasgow which was actually again taking little bits of muscle and looking them up under the microscope. These experiments under the microscope show that there were actual structural changes in the mitochondria. So we have evidence of biochemical abnormalities in the mitochondria from the magnetic resonance spectroscopy studies at Oxford, and structural abnormalities from the electron microscopy studies that were being done in Glasgow. So we know that this seems to be a problem with mitochondrial function in ME. Which may play a very important part in explaining why people have this very characteristic symptom of exercise-induced muscle fatigue, and sometimes pain in this illness.

Wetenschap voor Patiënten
(Science to patients)

On Thursday 10 April 2014 dr. Charles Shepherd answered questions in a chatwing-session. These are the Q&A of this session.

Q: Can you tell me exactly what the problems are with the mitochondria?
A: The mitochondria, which are the batteries in cells that help to produce chemical energy in the form known as ATP are not doing so in an efficient manner. It is possible that the initial viral infection, or other immune system stressor, has affected the way they work.

Q: In the overall mitochondria or just those of infected tissue?
A: Mitochondria are present in almost all tissues in the body - they are not just producing energy in muscle cells. Liver has a lot as well - but we have concentrated research efforts in relation to muscle mitochondria.

Q: Are the problems with mitochondria measurable/ provable?
A: Yes, you can look for evidence by taking a sample (biopsy) of muscle and looking for structural changes under the microscope. Professor Mina Behan has done this - including using some of my own muscle!
You can also look at changes in the way chemical reactions are taking place, including the excessive production of lactic acid, using what is called magnetic resonance spectroscopy (MRS). This has also been done on my own muscle - with results published in The Lancet!

Q: Will there be a test available in the near future to show one has problems with the mitochondria?
A: As I said earlier there are tests available - electron microscopy and MRS - that can show abnormalities in the mitochondria, or biochemical changes, that are consistent with mitochondrial dysfunction.

Q: I understand the tests are there for research purposes. But we need them to be on the common laboratory list of our GP's so they can ask for it.
A: I'm afraid these are research based investigations at present. Until the situation becomes more clear, and mitochondrial dysfunction is accepted by the wider medical profession, these tests are not going to form part of routine cynical assessment/diagnosis of ME/CFS.

Q: Is there a linear connection between the severity of the problems with the mitochondria and the severity of the fatigue, pain and other complaints?
A: The research that has been published so far has only involved small numbers of patients, and tended to avoid those with moderate or severe ME/CFS. So we don't have any clear evidence of a link between severity of findings and severity of symptoms.

Q: Is there a link between the increasing of the variable personal boundaries, the fatigue attacks, the muscle fatigue and the shortness of breath, dizziness, headache (orthostatic intolerance)?

A: Yes, all these problems are probably interlinked. I went to a really good physicians workshop on OI (causes, investigation, self-management, drug management) given by Professor Peter Rowe at the IACFS conference in San Francisco. I am currently writing this up for a website report.

Q: How come that the fatigue/exhaustion sometimes takes place a day or 2 days later? (I find this most unfair of ME/CFS, one moment you're busy, and a few hours later or the next day it turns out to have been too much again anyway).
A: The reasons why people have post-exertional malaise and symptom exacerbation are complex and were discussed in some detail in San Francisco. They probably relate to a combination of metabolic/chemical, immune system and possibly blood flow changes to skeletal muscle.

Q: For very severe cases, pacing is nearly impossible because they exceed their limitations by doing almost nothing. I'm almost always in PEM and I get worse and worse. Do you have any suggestions how severe ME-patients can try to stop deterioration? I can understand if you don't have answers.
A: I'm sorry but it's not really possible to go into how pacing should be applied to people with severe ME/CFS in just one line…The bottom line is that any sort of physical and mental activity has to be very low grade (keg passive exercises with a physic) and increased at a very gradual rate.

Q: But why is PEM sometimes 2 houres and sometimes 2 days later?
A: The simple answer is that we just don't know. The research that Professor VanNess et al has been doing (the double dose exercise test measuring Vo2 max) is shedding some light on what may be happening. The MEA is funding Prof Jo Nijs to carry out research into the cause of PEM.

Q: Why do you not mention HPV vaccination as a trigger for ME/CFS while you're mentioning many other vaccinations? Don't you known any cases that HPV is the trigger? Or are there other reasons or don't you acknowledge that HPV vaccination may be a trigger?
A: I have covered HPV in more detail on the YouTube video page for the mitochondria video (n39). I have a number of cases where HPV appears to have triggered ME/CFS but the MHRA here in the UK came to the conclusion that there is no link with this vaccine. I am sceptical about this conclusion.

Q: What do you think of oxygen therapy? Can it help with muscle pain or the problems with acid in the muscle?
A: Although there is evidence of hypoperfusion (low blood flow) in certain parts of the brain in ME/CFS I'm not convinced that oxygen therapy is of any value. There can also be dangerus in giving oxygen to people who may not be breathing in a normal manner. Evidence was presented in San Francisco that some people with ME/CFS have very shallow and low oxygen intake breathing because they do so via the abdomen instead of the diaphragm at the base of the chest. You can check your breathing by lying flat on the floor and observing whether it is diaphragmatic or abdominal - shallow or deep. Then try breathing in deeply for three seconds through the nose using the chest and diaphragm - the correct way to do so.

Q: How do you explain that the Japanese all of a sudden find evidence of inflammation, have pet-scans gotten better? And how would for instance scans of peeps with mild flu look like?

A: The Japanese are not the only research group to demonstrate what is called neuroinflammation. My post-mortem group here in the UK have evidence of what is called dorsal root ganglionitis in ME/CFS in tissue from people who have died. This finding has also been published.
The results we have published relate to 4 or 5 cases - would need to check with the paper for precise numbers. I have been discussing this post mortem research and the Japan research research on MEA Facebook if you want to follow it up. An abstract from our paper on DRG is there as well.

Q: Have you heard of stealth viruses?
A: Yes, stealth viruses were implicated in ME/CFS many years ago - but the virologists eventually came to the conclusion that they were not relevant.

Q: Do you think these viruses are relevant?
A: A wide variety of viral infections are capable of triggering ME/CFS and there is some evidence (from Dr Chia in California in particular in relation to enteroviral infection) that there could be persistent viral infection in some cases - as enteroviral infection persists in stomach tissue.
But I'm not convinced there is any link with stealth virus infection...

Q: Is ampligen dangerous?
A: Ampligen has side-effects, some of them can be unpleasant, but I would not say it was a dangerous drug. This is based on my reading. Ampligen is not available/licensed for use in the UK and I do not have any personal experience involving its use.

Q: Are you aware of the study of the University of Nijmegen where they are going to give the immunosupressant Anakinra to ME/cfs patients? What do you think of this?
A: I wasn't aware of the clinical trial you refer to but I do want to see trials involving drugs that can dampen down the immune system - because there is growing evidence of what we call immune system activation, and cytokine production, in ME.
One of the drugs that would fit into this category is Etanercept - which is used to dampen down activity in autoimmune disorders. I will need to translate the drug you refer to - it may be very similar.

Q: But wouldn't it be dangerous if people are not screened for infectious diseases like lyme? I hope they'll have mirtazapine on their hands to treat PML which might occur.
A: Yes, you have to be very careful about the sort of ME/CFS patients you use in clinical trials that involve drugs that can produce serious, or very serious side effects. The same logic applies to Rituximab - which can (rarely) cause a fatal allergic adverse reaction.

Q: Dr Shepherd, I'm deeply concerned about MEcfs discussions in the UK. How can the research collaborative be effective when members hold diametrically opposed views on what makes good science? Eg, PACE.
A: As you know I am a member of the UK ME/CFS Research Collaborative. I take the view that there is a case for having a forum where all sides of the ME/CFS debate can meet and discuss where we agree and disagree. We cannot go on with a situation where everyone sits in their own separate tents.

Q: I found the Stanford & IACFS/ME conferences very inspiring; How long do you think it will be before we see a break-through in #ME/cfs research?

A: Yes, there was a lot of good clinical and research information presented at San Fran - some of which has real practical implications for patient management. I was so inspired that instead of rushing out a report (7,600 words!) I've been spending the last week or so getting it right. I would not want to use the words breakthrough or cure but I think we are heading towards some significant steps in understanding the underlying causes of this illness. The work on neuroinflammation was particularly interesting and I am now discussing how we might try and replicate these PET scans here in the UK - a major hurdle is that these scans are very costly to do. And if we are dealing with a disease involving low level inflammation then we really need a trial of drugs that can dampen down this over-activity - in the same way that they are used to dampen down disease activity in rheumatoid arthritis etc.

Q: I'd love to read your conference report; I hope it'll be on the MEA website.
A: it is being prepared for the MEA magazine but I hope we will be placing it on the website as well for the benefit of non-members.

Q: Lately a MMA test showed a huge shortage of B12. Is there any link to ME?
A: We discussed B12 in San Francisco. There is no firm evidence of vitamin B12 deficiency in ME/CFS and no firm evidence of benefit from B12 injections. However, there are plenty of anecdotal/patient reports of people gaining benefit and one report demonstrating lowered levels in spinal fluid.

Wetenschap voor Patiënten
(Science to patients)

Seminar 40: ME & possible treatments

Dr. Charles Shepherd. Broadcast 21th April 2014

What are the most common symptoms in ME?

The most common symptoms in ME are I think grouped under three main headings: the brain symptoms and in particular here we have what we call cognitive dysfunctions. This is problems with normal mental activity, problems with short term memory, concentration, attention span, being able to process new information and retrieve information. Balance problems are a characteristic feature of this illness. People don't describe this as sort of feeling dizzy, spinning round, but they say that they feel as though they're constantly unsteady when they're walking along. As though they might be walking on rubber or so they probably had too much to drink. We know that the balance centers in the brain may be disturbed in this illness.

A third part of the brain abnormalities in this illness causing brain symptoms, is what we call symptoms relating to the autonomic nervous system. In medical jargon we call this orthostatic intolerance. This is problems related to being able to stand up for a long period of time. Or symptoms relating to changing posture from being flat or lying down to standing up. In which case there may be a change in or lowering of blood pressure causing what we call orthostatic hypotension; fall in blood pressure when changing posture. This causes problems such as feeling faint, sweating or even feeling sick.

So we have this group of important neurological symptoms, which I think fully justifies this disease being called a neurological illness by the WHO. We then have the very characteristic muscle symptoms which I already described, the exercise-induced muscle fatigue, pain which can be very severe in some people. It's not always present as muscle pain but muscle pain can be a very major feature of this illness. We then have what I call the infective immunological type symptoms; a feeling as though you got a sort of ongoing flu-like illness which may be accompanied by feelings of sore throats, enlarged glands.

And then finally, I think the other key symptom of this illness is the sleep disturbance. So I think you cannot have this illness without some form of sleep disturbance. It's interesting that in the very early stages this sleep disturbance may be an excessive requirement to sleep what we call hypersomnia, particularly in the early post viral stage. Then this quite often moves on to another type of sleep disturbance where people have either difficulty initiating sleep, getting off to sleep, they have erratic sleep, they wake up early in the morning. But they're no longer having to sleep 12-14 hours a day. Whatever type of sleep disturbance they have, they will describe the fact that they wake up and feel unrefreshed, they have unrefreshing sleep whatever type of sleep disturbance they have.

So those I think are the key cause symptoms of this illness. There are many other symptoms which are associated with it: increased sensitivity to light and noise, increased sensitivity to alcohol is a very interesting symptom which I think is diagnostic of this illness. But I think the brain, the muscle, the infective and the sleep symptoms are the core ones you would make the diagnosis on.

Which symptoms can be treated?

The symptoms that can be treated, and I think really should be treated by a doctor when they occur, are pain and sleep disturbance, and if it actually occurs as part of the illness then obviously any sort of depressive component. So as far as pain is concerned there are a number of drugs which doctors can consider prescribing when ordinary types of pain reliever like aspirin, brufen and paracetemol are found to be ineffective. And we have a, if you like this, step ladder of pain killing drugs available on prescription which could be considered when these sort of ordinary pain killers aren't working.

Examples of the sort of drugs which might be used, there is a drug called Amitriptyline, which is a sedating tricyclic anti-depressant drug, which is used at very low doses, not used as a depressive, the sort of dose you would use to treat a depression. It's used at a very low dose and at the very low dose it can help with pain, it can help with muscular pain, neuropathic nerve pain, and it can also - because it has a sedating effect - help with sleep disturbance. So that is one drug that can certainly be discussed with the patient. If pain is more severe then there are other drugs which pain relief doctors who are specialized in this type of medicine might consider using. One of which is called Gabapentin. This is a drug which is actually normally used to treat epilepsy, but it's also been found, again as a different type of dose and regime, to be very helpful and sometimes in pain relief particularly pain relief when that involves nerve pain.

There are various drugs which can help with sleep disturbance in addition to possibly Amitriptyline. There are groups of drugs which can help people, there are short acting drugs, they can help people get off to sleep and they are just used for a very short period of time. There is also some evidence that the drug melatonin, which is used to help people cope with jetlag, can be helpful in some people with this illness. And people with this illness who have a very disturbed form of sleep disturbance, sometimes they gather a complete reversal of sleep rhythm, that is something that could be considered in those circumstances. And as I say if someone has a clinical depression with this illness, and a clinical depression is something that can occur with any long-term illness, especially when you're having all the problems that you're having with an illness like ME, then that always has to be taken seriously. Because we know that sadly some people with ME who are very upset because of all the things that are happening around them, do actually contemplate and just occasionally even commit suicide.

So depression, clinical, true clinical depression as opposed to just feeling fed up with this illness must be taken seriously. And again if necessary treated with antidepressants. Sadly at the same time we have groups of symptoms which are not amenable to drug treatment. One example there would be the problems that people have with cognitive function, problems with memory, concentration and it would be wonderful if we as doctors had some sort of drug that we could help people with that type of symptom cope with better.

What other treatment suggestions can you give?

Other treatments in addition to the key aspects of management which of course are activity management and pacing and dealing with symptoms such as pain and sleep disturbance are, I think that any doctor who is dealing with this illness has to deal with the many practical aspects that this illness creates for their patients. So I think they have to be very pro-active and supportive in relation to things like helping them with their benefit applications, giving them a suitable advice on what they should do in relation to work and employment. And in the case of children and adolescents helping them with their education which might involve trying to get home tuition, if a child is able to do so, and integration back into school at a very gradual level if the child is well enough to start returning to school.

What help can be given to very severe ME-patients?

Help for people with severe ME is very sadly lacking, certainly here in the UK, and I suspect the same picture applies throughout the rest of Europe. Many of these people who are wheelchair bound, house bound or bed bound have no access to medical services. They are unable to get to hospital clinics for appointments obviously and at the same point we have a number of specialist referral hospitals based services here in the UK now, but these clinics by and large are not providing home visiting domiciliary services for people with severe ME. So there is a major problem for this group of patients in accessing medical services and it is something that really should be addressed as a matter of urgency. We have tried to do that through the all-party parliamentary group on ME, but it very much relates to the willingness of physicians and people looking after patients at a hospital based level to try and set this in motion, And sadly that is not happening.

Wetenschap voor Patiënten

(Science to patients)

On Thursday April 24th 2014 dr. Charles Shepherd answered questions in a chatwing-session. These are the Q&A of this session.

Q: In your webinar you mentioned several symptoms of ME. But you did not mention problems with the stomach or the bowels. Don't you consider problems with them as symptoms of ME?
A: Yes, irritable bowel type symptoms are very common in people with ME/CFS and I have just produced a new information leaflet on this subject for people in the UK. However, it's also important to exclude other possible explanations - such as coeliac disease. Although very common I would not regard irritable bowel type symptoms as being a key diagnostic feature of ME or CFS.

Q: Do you have personal experience with alternative treatments or did you hear of them from patients? What is your opinion about them?
A: There is a limited role for alternative treatments for bowel symptoms. One product that may be worth trying is a probiotic such as Activia - where there is some research evidence of benefit for constipation and pain. Ginger and acupressure at the wrist can also help where nausea is a problem.

Q: What is Activia, is it a medication?
A: Activia is a probiotic supplement that contains bifidobacteria - and it may help where there is constipation and pain.

Q: Do you know a treatment for problems with the bowel? (and coeliac disease is excluded)
A: After excluding other possible explanations most doctors would recommend a symptomatic approach using drugs that can reduce constipation or diarrhoea, colic pain and wind/bloating. Changes to diet can also be very helpful in some cases, especially for wind and bloating.

Q: I saw a video of Teitelbaum who, like you, said that if you don't have problems with sleeping you don't have ME. Don't most of the criteria mention "unrefreshing sleep", which imo is something different?
A: I would regard unrefreshing sleep as a key diagnostic feature of ME/CFS. Disturbed sleep can take several forms in ME/CFS - in the early stages there is often an excessive sleep requirement - known as hypersomnia. Later on people may have difficulty getting to sleep or just very erratic sleep.

Q: Teitelbaum also said that something like 90% recovers, doesn't he mean they manage it with diets and pills?
A: I would not agree that 90% of people recover from ME/CFS. A lot of people make some improvement (as I have done) and learn to manage their symptoms and disability. But that is

not the same as recovery. A significant minority - perhaps as high as 25% - are severely affected and remain so.

Q: Once an orthomolecular doctor noticed that my system had shortage of hormones from the adrenal cortex like DHEA. He suggested to take medication containing those hormones. Would you give such treatment? Can it possibly harm the whole system?
A: There is plenty of good quality research evidence to show that people with ME/CFS have slightly lowered output of the hormone called cortisol - but clinical trials have not shown that taking cortisol is a safe and effective form of treatment for ME/CFS. There is no sound research evidence to show that people with ME/CFS have lowered levels of DHEA and there are dangers in taking DHEA if it is not needed by the body - so I would not recommend this approach.
A research study from Cleare et al. in 2004 reported that DHEA levels were actually raised in ME/CFS -suggesting that DHEA supplementation was both unnecessary and possibly harmful.

Q: I have been an ME/CFS patient for about 30 years and my question is: I'm reading regularly that the pituitary gland probably plays a role in ME/CFS. The pituitary gland controls the thyroid gland. Could it be that a thyroid abnormality is an effect/symptom of ME/CFS ? Or vice versa, that ME/CFS is an effect/symptom of a thyroid abnormality, like for example subclinical hypothyroidism?
A: We know there is a disturbance in the hormone regulating pathway that starts in the hypothalamus gland in the brain, the pituitary gland (which lies beneath it) and the adrenal glands (that produce cortisol). But there is no sound evidence of a similar disturbance taking place in the thyroxine pathway.
So doctors should not be prescribing thyroxine to people with ME/CFS - unless they also have abnormal blood tests (T4 and TSH levels) that are used to measure thyroid gland function.

Q: Can alternative treatments in general cause harm to ME/CVS patients?
A: I would not say that alternative treatments cause harm to people with ME/CFS , but they have to be used with care, especially if you are going to take large doses of supplements or vitamins or plant based remedies.
And if you have faith in things like acupuncture (especially for pain) or homoeopathy then I think they are well worth trying.

Q: Is there a relationship between ME/CFS and a vitamin B12 deficiency? I have both an elevated TSH value as a far too low vitamin b12 value. I am recently treated with vitamin b12 injections and Thyrax.
A: Having an elevated level of thyroid stimulating hormone (TSH) normally indicates that your thyroid gland isn't working as effectively as it should be. Thyroid disease and vitamin B12 deficiency can sometimes be linked through autoimmunity - where the immune system attacks the body's own tissues.

Q: Are you familiar with low dose naltrexone? What do you think of?
A: Some people in the UK are prescribed LDN and we receive very mixed feedback from them. The problem is lack of evidence from a clinical trial to show that it is a safe and effective form of treatment. So in our current state of knowledge I do not use or recommend LDN. There has been a small clinical trial using LDN in fibromyalgia (Younger et al, 2013) which suggested that it provided some benefit in pain relief.

Q: Big compliment btw for the video on exercise (and mitochondria).Iif anyone ever starts again about treadmills I'll show it to them!
A: Thanks for the comment on the activity management video. There is a new research study out confirming that the VO2 max test is a useful tool for clinical assessment in ME/CFS.

Q: Speaking of videos, last time I mentioned a pressure in my brain after antibiotics etc. It sometimes moves to my eyes (they tremble, which can also be felt from the outside) and for instance my throat/thyroid, which "plops", also noticeable by others and I filmed it. Would you care to watch it? A neurologist said they‘re muscle contractions, but as far as I know I don't have muscles in my brain.
A: Ah, but you do. There are lots of small muscles controlling movements in the face, eyes, mouth etc. A spasm in the muscles that open/shut your eyelids is called blepharospasm - and I think it's quite common in people with ME/CFS, especially when they are tired.

Wetenschap voor Patiënten

(Science to patients)

Seminar 41: Promising discoveries and research

Dr. Charles Shepherd. Broadcast May 5th 2014

Which are the most important discoveries of last years regarding ME?
When it comes to important discoveries in the past few years I think, apart from the very interesting results from the clinical trial of the drug Rituximab, it is very difficult to isolate anything and say that is a major breakthrough in our understanding of this illness, that is a major piece of the ME jigsaw fitting into place. I think what we are seeing at the moment is a number of small pieces of this ME/cfs jigsaw starting to fit into place. So these are pieces of information, such as I say, rather like pieces of a jigsaw in relation to what is going on in the brain.

And in particular here I think I would like to highlight the work of Professor Julia Newton up in Newcastle here in the UK who has done some really solid work on the role of what we call this autonomic nervous system, this division of the nervous system that helps to control blood vessels. It also has a role in gut activity, bladder activity and even blood supply to the skeletal muscle. And it may well be that the disturbance in autonomic nervous system activity, and the results of the research that is going on in Newcastle, is going to help us get a much better understanding of what may actually be going wrong in skeletal muscle and also possible blood supply to the brain and the way in which perhaps decreased blood supply to the brain because of the autonomic nervous system dysfunction is causing these symptoms like cognitive dysfunction with short term memory, attention span and concentration being very poor in these patients. Because that is an area where we really do need to make some headway.

In addition to that, other pieces if you like of this jigsaw which is starting to fit into place, is the role of the immune system. And I think we are starting to change our mind about the role of the immune system in this illness. There used to be a feeling that the immune system abnormalities, which have not always been consistent or robust, were pointing to some sort of immune system deficiency in this illness, a defective immune system response. Whereas the sort of picture that is now emerging is of an immune system which may be, as a result of this viral infection that triggers the illness off, acting in a rather overactive state. So that there is in medical jargon low-level immune activation taking place.

And one result of this is the production of immune system chemicals called cytokines. These are the immune system chemicals that you normally produce when you've got an infection, a flu-like infection that make you feel so grotty. It is not the virus itself that makes you feel flu-like, it's the cytokines. And it is possible that these cytokines being produced at a long going basis as a low-level of producing these sort of ongoing flu-like symptoms, malaise and

everything else that goes with having ME. At the same time we now have drugs and this is taking us on to possible forms of treatment which can actually dampen down this cytokine activity.

So I think by piecing these bits of muscle, brain, immune system, genetic factors together, we're starting to build up a more solid picture of what is going on in this illness. And I don't think we're going to find in the future that there's going to be some sudden breakthrough, a major piece of research which suddenly explains all this. It is going to be very much a question of providing further bits of information, further bits of this ME jigsaw and putting them into place and fitting them together. Because all these different abnormalities are probably interacting to a certain degree.

What is the MRC and what is its research program?

The MRC or Medical Research Council is the government body here in the UK that sits on a very large pot of money for medical and scientific research. And, as I'm sure is the case in many other European countries, there has been considerable criticism from the patient community and also from politicians about the lack of research into the biomedical causes of ME.

Now up until recently the Medical Research Council I have to say took very little notice of these complaints and concerns, but about 3-4 years ago it decided it would set up an expert group on ME/cfs research and I was a member of this group and it was a very welcome move. It was something that I would certainly recommend to people who are campaigning to try and get government-funded research elsewhere.

So we had an expert group with a remit to identify a list of high-priority and medium-priority research items which it was felt should then be encouraged from the point of view of getting researchers to submit research applications to the MRC. So we identified these research priorities involving muscle, brain, immune system, sleep disturbance, genetics and one or two other subjects and invited applications from the research community. And what was so welcome about this process was that we didn't expect that many research applications to come in. But in actual fact we got far more research applications than there was money available for.

A total sum of about 1.5 million pounds of ring-fenced money was made available for these research grants. And with very few exceptions these were very high quality research applications. In addition to that many of them involve people who were totally new to this subject. So it was I think a very welcome and very productive exercise. And in the end 1.5 million pounds of government research money was distributed to five projects and we have five projects now underway. There is a study on sleep disturbance and also a drug treatment is being trialed for use in sleep disturbance in ME as part of that study.

We have a study at the University of Liverpool which is taking forward the research on mitochondrial disturbance in skeletal muscle. We have a study looking for biomarkers, is there a biomarker , a blood abnormality which can be related to debilitating fatigue. And this is starting off using patients with a very well-defined condition called Sjogren syndrome in which central fatigue is often very prominent feature and it has a number of overlaps with ME/cfs.

And then we have a study on immune system functioning in ME and this goes back to the point I was making about immune system activation in this illness and the production of these immune system chemicals. We know that when people with an illness called hepatitis

C are treated with interferon, which is one of these immune system chemicals, they can actually develop an ME like illness as a side effect. So this study on the immune system function and possible low-level activation of the immune system in ME is going to look at this group of people who are being treated with interferon for hepatitis and see what differences there are between the group who do not develop ME/cfs-like symptoms and the people who do develop ME/cfs-like symptoms when they are treated with interferon.

And then the final study is a further study on autonomic nervous system dysfunction. This is this part of the nervous system which controls blood flow, blood vessels, pulse, heart rate, and this will take forward some of the very important research that professor Julia Newton and her colleagues in the university of Newcastle are already doing in this area. So that's five very important studies now being financed by the Medical Research Council here in the UK.

Wetenschap voor Patiënten
(Science to patients)

On Thursday May 15th 2014 dr. Charles Shepherd answered questions in a chatwing-session. These are the Q&A of this session.

Q: You spoke about 'post exertional malaise' in ME following physical exercise. What about 'PEM' after mental exertion and after sensory 'overload'? For me the effects are the same.
A: Actually, I think post exertional exacerbation of symptoms is a better description. Although this primarily follows physical exertion it can also follow mental exertion. The MEA is currently funding Prof Jo Nijs et al to try and get a better understanding of what causes PEM/PEE.

Q: You mention that it may be possible to take medicines in order to reduce cytokines with as result less problems like flu, sore throat etc. But would it not be a danger to become overactive when you do not feel the symptoms any longer?
A: There are a number of drugs that can help to 'dampen down' immune system activation and over-production of cytokines. One such drug is Etanercept - and there is already some limited evidence from a small study in relation to ME/CFS.
I think you have to be fairly cautious for a while about physical activity levels, and to some extent mental activity levels, once symptoms have either stabilised or there has been a significant degree of improvement/symptom reduction in ME/CFS.

Q: Does the fact that the MRC decided to finance the research mean that your Government recognise ME (CVS) as a biomedical disease?
A: The MRC have fully accepted the need for funding biomedical research (which they are doing) and have highlighted the need for research into neuro inflammation in particular. However, the UK government position still remains rather neutral in that while they fully accept ME/CFS to be a genuine and debilitating illness, official bodies like NICE (who control what doctors prescribe) view this as an illness that involves both physical and psychological causation.

Q: In webinar 36 you talk about dysfunctions of the brains which are measurable. Which dysfunctions, and are they measurable, in the sense that in that case we patients can effectively confront our GP's with them when consulting them?
A: I'm afraid that all these sophisticated (and often quite expensive) tests that can measure aspects of brain dysfunction are hospital based - so you are not going to get them through primary care or a GP. Most are also research based rather than being available for routine clinical assessment of patients. One possible exception is tilt table testing - which can be very helpful in assessing people who are having blood pressure and pulse rate problems when they move from lying to standing - what is called orthostatic hypotension (fall in blood pressure when standing up) or POTS (postural orthostatic tachycardia syndrome). Orthostatic intolerance/hypotension causes symptoms such as feeling faint or lightheaded when staying up - along with nausea, sweating, reduced concentration, blurred vision…….it is very common in ME/CFS but often unrecognised and not managed properly by doctors!

Q: So by taking those medications to dampen down the cytokines we can get rid of the everlasting flu-like symptoms, but we must still remain cautious with activity. To me it seems

difficult to find a new measure for activity, as it is now given by sore throat etc.
A: There are now a number of investigations, neuroimaging in particular, that can demonstrate abnormalities in the way that parts of the brain control the output of hormones (low cortisol in particular), blood flow (SPECT scans), cognitive function (functional MRI scans) and activity in what is called the autonomic system.

Q: Is it common with brain-fasciculations to have neurotransmitters coming out of your ears?
A: I'm not quite sure what you mean about having neurotransmitters coming out of your ears! Fasciculations can refer to visible twitching or trembling of muscles. In ME/CFS it is sometimes seen in the tiny muscles that control the eyelid movement - something called blepharospasm.

Q: Mere muscle contractions don't cause high-ness or things "breaking" in your brain?
A: There isn't any evidence to show that these visible muscle contractions/fasciculations are causing harm or damage in the brain - even though they are very annoying.

Q: How did you motivate the MRC to decide to pay the research? Or in other words: what can we learn in other countries from your approach?
A: About 5 years ago the MRC was persuaded by politicians and patient groups to address biomedical research - so they set up an MRC Expert Group on ME/CFS research. I was a member of the group. The Expert Group then listed a number of biomedical research priorities. The MRC responded positively by providing £1.5 million of ring-fenced funding for biomedical research on our priority list. Five studies - central fatigue biomarkers, immunological activation, autonomic system, mitochondrial function and sleep intervention with sodium oxybate - were accepted and these are all now in progress.

Q: Your answer makes clear the important role of organised and joined patient groups!!
A: Here in the UK we have an All Party Parliamentary Group on ME at the House of Commons - it is a very useful way of making sure that Ministers and senior officials from MRC, NICE etc. have to come and answer difficult questions. Do you have anything similar with the Dutch politicians?
Q: I know the different patient groups in the Netherlands already know the need of attention by politicians and journalism. And I thank them a lot for doing so!!! But your words make clear once again the importance of doing so and trying to improve.

Q: Is there something in general to tell about problems for ME-patients with their weight?
A: Weight gain is very common in ME/CFS but when this occurs it's worth having thyroid function checked if this isn't adding to the problem.
Unfortunately, there is also evidence to suggest that being overweight can have an effect on the underlying disease process in ME/CFS because it is now known that fatty tissue is a source of inflammatory immune system chemicals - which may help to explain why heart disease and diabetes are more common in people who are overweight.

Q: Elsewhere in the webinars you talked about the hypothalamus. What's the impact of the hypothalamus with ME-patients?
A: Hypothalamus is a tiny pea like gland in the brain that helps to control temperature regulation (which probably explains why people with ME/CFS have problems with high/low temperatures). It also send messages to all the glands in the body that produce hormones - which may be involved with lowered output of cortisol.

Q: Are there any drugs or supplements to regulate the functioning of the hypothalamus?
A: Unfortunately, we don't have any drugs that are really useful in helping to reset the hypothalamus when it's not functioning properly.

Wetenschap voor Patiënten
(Science to patients)

Seminar 42: State of affairs regarding ME

Dr. Charles Shepherd. Broadcast May 19th 2014

What will help to get recognition of ME as a biomedical disease?

There are two important things that we need to do in order to get proper recognition from the medical profession for ME being a biomedical disorder. The first thing is that we have to identify some robust and consistent, what we call biomarkers, to make a diagnosis of this disease. As I've been saying earlier, we don't have blood tests which you can diagnose ME through. If we can get some biomarkers of abnormalities in the blood in relation to the immune system or the endocrine, the hormone producing system, or any other system which are consistent in people with ME, which are not found in people who are normal and healthy, are not found in people with other diseases, then we have evidence of this being a physical disease.

The second thing that we must have is consistent evidence of abnormalities in the muscle, the immune system, or the brain which are consistent with symptoms. Because at the moment we have a number of abnormalities which are quite clearly described in the literature, but they don't necessarily are linked to symptoms. We can make assumptions that they may relate to symptoms just like we can say that low blood pressure, low blood volume to the brain may be causing cognitive dysfunction. But we haven't proven that. And until we can come back to the medical profession with firm evidence in this sort of area and say here is a abnormality in the brain, it's clearly linked to that particular symptom, then we are going to make real progress in persuading sceptical medical colleagues of mine that this is a real physical illness.

Which current developments are hopeful?

Current developments which I think are really helpful in taking this illness forward from the research point of view, certainly in addition to the research initiatives that I've already been describing from the MRC and bodies such as that. But I think the real positive aspect of research at the moment is the way that people are cooperating, starting to cooperate on an international basis. Because up till now we've had a lot of different people in different countries getting on with their own research. But I think we are now reaching the point where we are meeting together, discussing research that's taking place and cooperating on research. Certainly one example of this is the way that the biobank that we set up at UCL is cooperating with the Norwegian biobank.

We're using similar types of protocols, we're using similar types of criteria for diagnosing the people who are giving the blood samples. And one aspect to this that I think is very encouraging is the work that Dr. Andy Kogelnik over in the States is putting into this, and the

Open Medicine Institute, the OMI. I was lucky enough to be invited to go over to New York last year, to participate in the two, three day meeting that we held. This was a round table meeting of experts. Researchers and clinicians from all parts of the world who just got together, we were cocooned if you like, in a hotel for three days and we just discussed research. Tossed around a lot of ideas and came up with things which really needed to be done and needed to be funded. And it wasn't just talk. Andy is gone off and put these ideas out on the internet and money is starting to come in, and people are starting to discuss and cooperate as a result of that.

I think another important development in a similar way but within the UK is the development of what we call the UK research collaborative, which is an offshoot of the MRC expert group on ME/cfs research. And this is an umbrella organization that is bringing together existing researchers, new researchers, people who are interested in getting involved with this research, charities, people who are funding research like the MRC and the NIHR, as well as – and this is very much a missing link in research at the moment – the pharmaceutical companies.

So we're all meeting together as one body to discuss research. We're planning a major two day conference next year, to take this forward. And I think that's again something that people in other countries could look at and perhaps do something very similar to bring everyone together within a country, who's involved in any sort of research or funding research to actually meet and discuss what's going on.

What hope can you give to the most severe ME-patients?

I believe there is real hope now for the people who are at the most severe end of the spectrum of this illness, who are bed bound, wheelchair bound or house bound. Firstly because, as I'm being saying, we are starting to make real progress in piecing together what are the various aspects that are causing this disease. As we understand more about what is causing this disease, we are now gonna start looking and we are looking at treatments like Rituximab, and things, drugs which actually act on the underlying disease process. It's opposed to just trying to patch things up by treating symptoms.

At the same time I know progress is very slow and there is an urgent need to make things much quicker. But there is a recognition from the people who are working in the clinics, the hospital based clinics, that the severely affected are not getting a fair deal. That they need to provide some sort of specialized inpatient facilities where people with severe ME can be looked at in a sympathetic environment where they can be properly assessed, where any management interventions could be looked at in a careful and sympathetic way.

And where this is not possible that there needs to be domiciliary home based services where the hospital goes out to the person with severe ME and deals with them at home. Because it is clearly just not acceptable that a whole group of people with this illness are just totally divorced from the normal health service and social care services that are available to everyone else in this country. And to whom people with severe ME have paid for and they're now getting absolutely nothing in return.

Wetenschap voor Patiënten
(Science to patients)

On Thursday May 22th 2014 dr. Charles Shepherd answered questions in a chatwing-session. These are the Q&A of this session.

Q: I am thinking of trying LDN. What is your opinion on LDN?
A: We receive quite a lot of anecdotal information about LDN. Some people say it helps; a significant number report no significant benefit and a few say it makes them worse. It is not a drug that I would want to recommend or use until we have sound evidence of safety and efficacy from a proper clinical trial. I would add there there is evidence of some benefit from using LDN in a small clinical trial carried out in patients with fibromyalgia.

Q: I have also neuropathic pain (allodynia/hyperesthesia). Is LDN tested for this condition?
A: I don't think there is any sound evidence relating to relief of neuropathic (nerve) pain from clinical trials for LDN. But there are some useful drugs of proven benefit for nerve pain - examples include gabapentin and pregabalin.

Q: In your college you mention that a very important step forward would be to find a/ some biomarkers. Could cytokines be usefull as biomarker?
A: Yes, it's possible that cytokines, or a combination of cytokine abnormalities, could act as a diagnostic biomarker for ME/CFS. And there is some evidence that this is the case from Jose Montoya's research group in Stanford, California. This work was presented at the IACFS/ME conference in March. I have done an on-line 16 page supplement report on the conference. It can be downloaded from the MEA website: www.meassociation.org.uk

Q: Is it a requirement for new research that that patients that are exemined are diagnosed according to the International Consensus Criteria? Are they assumed to be the point of departure?
A: I don't know of any research groups who are currently using ICC for recruiting patients into research studies. Most studies are still using Fukuda or Fukuda + Canadian criteria - which is what we are doing for recruitment into the ME (blood sample) Biobank in London.

Q: You spoke earlier about the 'encephalomyelitis' in the name ME and the lack of evidence for using this name. It seems that some studies, like the recent study (Watanabe et al.) using PET scanning did show that neuro-inflammation is present in patients with ME.
A: Yes, the Japanese study indicates neuroinflammation - as does the post mortem studies I was involved with where dorsal root ganglionitis was found in some of our post-mortem cases. But neuroinflammation can occur in a variety of conditions that are not even classified as neurological - e.g. lupus.
So the presence of neuroinflammation does not automatically mean that someone has an encephalitis - which would mean a more severe and widespread inflammation of brain tissue and would be found at post-mortem

Q: Do you still want to use Encephalopathy instead of Encephalomyelitis. Despite the fact that there's been a study in Japan that shows that in every ME patient that was participating there was inflammation of the brain.
A: We have not found encephalitis or myelitis (= inflammation in the spinal cord) in any of the post-mortem cases. So I still think that M encephalopathy is a better term to use. Encephalopathy is also a term that most doctors are willing to accept, including those who will not use encephalomyelitis!

Q: There is recognition that the severe patients need specialised facilities. Does that mean that this kind of assistance is already organised and operational?
A: I'm afraid there is very little in the way of in-patient hospital based services for assessment and management of people with severe ME here in the UK. And there aren't any domiciliary (home visiting) services either. This is an unacceptable gap in health care for people with severe ME.

Q: Would it not give much more clarity if only the ICC-diagnosis was used for research?
A: It would add much more clarity if researchers agreed on a single case definition for ME/CFS. As Prof Lenny Jason pointed out in San Francisco we now have over 20 case definitions and no real agreement on which one to use.

Q: Last time you told that many ME-patients have overweight. Is this just due to the fact of lack of exercise or doe other factors play a rol in this?
A: There are a number of factors that are probably involved but lack of activity combined with no change in diet must be a major factor. It's very important that people who are gaining weight with ME should have their thyroid function checked - because low thyroid function can cause weight gain.

Q: For very severe cases, pacing is nearly impossible because they exceed their limitations by doing almost nothing. I'm almost always in PEM and I get worse and worse. Do you have any suggestions how severe ME-patients can try to stop deterioration? I can understand if you don't have answers.
A: I'm afraid I don't have any simple answers regarding the problems facing people with severe ME. What I will say is that progressive deterioration is unusual in ME/CFS and where it occurs there should always be a thorough clinical reassessment to make sure that nothing else medical is being missed.

Q: The situation in the Netherlands for severe patients is not better then in the UK. Improvement will come from recognition, based on research. So please continu all the research you planned to do!!!
A: There is also a major problem in the way that people with severe ME are not being involved in research. But things are changing…..
The ME Biobank in London is actively recruiting volunteers with severe ME to give blood samples. And Prof Julia Newton, in Newcastle, who is appearing next, has been given a grant from MERUK to carry out a study on people with severe ME. This will involve visiting these people at home.

Q: Last time you asked if we have in the Netherlands a similar system of the All Party Parliamentary Group on ME. I'm not sure, but I do not think that we have such a Group. But it seems to me a very significant way to influence and inform the Government. Thanks for the idea!
A: Regarding all Party Parliamentary Groups - I suggest you see if a similar system operates

in the Netherlands. If it does, you need to find a friendly MP who is interested in ME/CFS and set up a group - which can then question ministers, civil servants, health authorities etc.

Q: How come that side effects of regular meds like antibiotics, inflammatory agents etc are becoming more invalidating throughout the years?
A: I'm not sure if I understand your question about antibiotics and the way you are using invalidating. Do you mean the side -effects are becoming more prominent?
People with ME/CFS are certainly more sensitive to some types of drugs, especially those like antidepressants and some types of painkillers that act on chemical transmitter systems in the brain. But the reasons why remain unclear...

Q: Let's take the side-effects first. They tend to become worse throughout the years, aren't they?
A: I'm not sure that the actual side-effects of established drugs have become worse. I think there is increased recognition that people with ME/CFs are more likely to experience side-effects with some types of drugs. On the other hand, people with ME/CFs who use drugs like amitriptyline for pain relief or sleep disturbance often report that side-effects tend to gradually diminish as time goes on.

Q: With triptans their condition can get worse, isn't it? Also with benzodiazepines, but that's due to habituation?
A: Yes, there are some drugs, including benzodiazepines like Valium, that came make people with ME/CFS feel worse. Statins for lowering cholesterol also have to be used with care because one of their side effects is to cause muscle damage/pain.

Q: Also I hear complaints that a certain med has worked for years, and then all of a sudden doesn't seem to have its desired effect anymore. Is that explicable?
A: The fact that some medicines become less effective, or ineffective, over a period of time is not something that is unique to ME/CFS.

Q: Would you suggest to use only the ICC?
A: the ICC has some advantages as a clinical definition but I sense there is great reluctance amongst international researchers to move to using either this or the Canadian criteria. What we have to work on is international agreement on a research definition that EVERYONE starts to use.
It makes no sense whatsoever to have over 20 different case definitions for ME/CFS in use - especially when it comes to trying to compare the results of different research studies on the same subject but where different types of patients have been used.
And I am not blameless here having helped to produce and revise the London criteria for ME!

Q: So all researchers need worldwide consensus criteria. Is there a leading group/researcher that can propose criteria and convince everybody to use them?
A: I hope you have heard of Prof Lenny Jason from Chicago - who is the real expert here. If everyone would listen to what Lenny is saying, which includes constructive criticism of several case definitions, things would really start to improve….
Lenny Jason has a wonderful powerpoint slide showing a house of playing cards crumbling because the foundations are unsound. The same applies to ME/CFS - unless you have a sound foundation of an agreed case definition everything else that relies on it - cause, management, epidemiology - will fail.

Q: Do you know if there are plans to r replicate the PET findings of Japan somewhere around the world?
A: I am currently discussing with some of my neurological colleagues whether we can set up a UK study that would aim to replicate the Japanese findings. A major problem here is cost - this type of PET scan is extremely costly.

Q: Do you have a patient organisation on brain problems? Those organisations sometimes have the money.
A: We don't have any 'brain organisations' or brain charities here in the UK that would be sympathetic to funding a neuroimaging study in ME/CFS.

Q: Is drug clearance less in people with ME due to liver cytochrome P450 system or kidney function or maybe methylation problems? Or do people need lower blood values for drugs to work?
A: I don't think there is any sound research evidence to show that people with ME/CFS have problems with metabolism of drugs in the liver or their excretion/removal via the kidneys.