



An interview with Dr Charles Shepherd:

Orchestra's, Elephants, Jigsaw puzzles and Mountains!

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By Helen Hyland, Fundraising Manager, ME Association.

In this recent interview, Dr Shepherd explains why M.E. research is so important, and why he is asking for your support for the [Ramsay Research Fund Christmas Appeal](#).

Helen writes:

Keeping up with Dr Charles Shepherd when he is in full flow is almost impossible. His enthusiasm about research into M.E. is infectious.

He knows so much, he's involved in so many different areas, and he's so eager to tell you all about it. All at the same time.

He's like a fountain bubbling over with knowledge. And you never quite know where your conversation will take you.

Dr Shepherd is the ME Association's medical adviser, trustee and spokesman. He is a passionate advocate for and about all things to do with this devastating disease.



Dr Shepherd in 2018 BBC Newsbeat Documentary

He works relentlessly – and on a voluntary basis – lecturing, being interviewed by the media, providing medical and research information, campaigning, networking, and leading vital research via the MEA [Ramsay Research Fund](#).

Our conversation about M.E. research (and the need for more of it) took us from an orchestra, via elephants, to jigsaws and mountains.

From which you'll understand that research into M.E. (myalgic encephalopathy/encephalomyelitis) is no easy subject to grasp and why this piece should perhaps be subtitled "M.E. Research for Dummies" – and I freely admit I'm the dummy!

So, what did I learn?

- Biomedical research has come a long way although it might not seem like it at times.
- Dr Shepherd is confident we are moving in the right direction, especially now that the [UK ME/CFS Biobank is open for business](#) and stimulating new research at home and abroad.
- We still have a long way to go and quick fixes are unlikely. Sadly.
- More funding will mean more projects, more knowledge, and a clearer understanding of what is triggering and perpetuating M.E. Hence Dr Shepherd's personal plea for your support for the MEA [Ramsay Research Fund Christmas Appeal](#).

I asked what research has taught us so far. Dr Shepherd used the "3P's" to explain distinct stages of how M.E. might develop: predisposition, precipitation and perpetuation.

He said that there is a growing body of evidence that suggests people in some families are **predisposed** to getting M.E. because of their genetic makeup. And whilst many cases of M.E. are **precipitated** (or triggered) by an event –



usually a viral infection (but also trauma, vaccination, or exposure to toxins), undue physical or mental stress at the time can also play a part in some instances.

An orchestra?

M.E. is an illness that is **perpetuated** by the interaction of a number of components that include:

- ongoing activation or dysfunction of the immune system;
- problems with muscle and mitochondria;
- chemical abnormalities at the cellular level (metabolites and enzymes);
- disturbances in the neuro-endocrine (hormone) system,
- brain abnormalities (the autonomic nervous system, hypothalamic dysfunction (the ‘brain thermostat’ that controls temperature regulation, appetite and sleep patterns) and [activation of microglia with low level inflammation](#)).

It is this perpetuation that makes M.E. [“the last medical enigma of the 21st century”](#).

M.E. is an illness that affects many interrelated parts of the body; something that happens in one place, will affect other parts as well.

Dr Shepherd likened the body to an orchestra: all the different systems (i.e. brain, heart, gut, immune system) have a part to play and, with M.E., if something isn’t quite right in one system, then this will affect other systems if not the whole body too.

The UK ME/CFS Biobank

He highlighted the growing body of detailed work that focusses on investigating these complex interrelationships. Key to the development of our knowledge is the UK ME/CFS Biobank which the ME Association worked so hard to establish.

Dr Shepherd is clearly and justifiably proud of this achievement and is determined that the ME Association will do all it can to support its operation and anticipated growth.

The Biobank is a project that is close to his heart and Dr Shepherd is chair of the steering committee. He pointedly reminded me that the ME Association is now the only M.E. charity in the UK to fund the ongoing costs of the Biobank.



Dr Shepherd is Chair of the Biobank Steering Group

And the Biobank isn’t just about collecting and storing samples. The team of experts led by Dr Luis Nacul has been very successful with research in their own right. This has included securing several high-profile grants from the National Institutes of Health (NIH) in America.

One for a study that Dr Shepherd described as offering, “the most comprehensive study of the [immune system](#) to date and biggest ever single investment in biomedical research to happen in the UK.”

This huge (\$2.1m) award is enabling the Biobank team to look in unprecedented detail at both ambulatory and severe cases (because blood samples have been collected from people with M.E. in their own homes) and to include comprehensive clinical data and in-depth immunological profiling.

Dr Shepherd described what went on in the body's immune system as "an orchestra of different components" (which might include: antibodies, auto-antibodies, T cells, B cells, helper cells, natural killer cells, immunoglobulins, gamma globulins....).

The study will hopefully give us the best picture yet of what is actually going wrong in the cellular element of 'the immune system orchestra'. This could then provide clues as to what kind of immune system treatments we should be working towards, and what drugs we could be testing to dampen down any immune activation or abnormality for example.

I could tell that Dr Shepherd was bursting to tell me more but was constrained by his promise to keep the preliminary findings confidential. He didn't want to steal the Biobank's thunder or jeopardise publication. But hopefully we'll see the results in the new year.

He then pointed to another NIH funded study at the Biobank that will look at the role of infection and particularly latent (dormant) viral infections that appeared to be reactivated because of immune dysfunction in M.E. Again, we should hear more about this research in 2019.

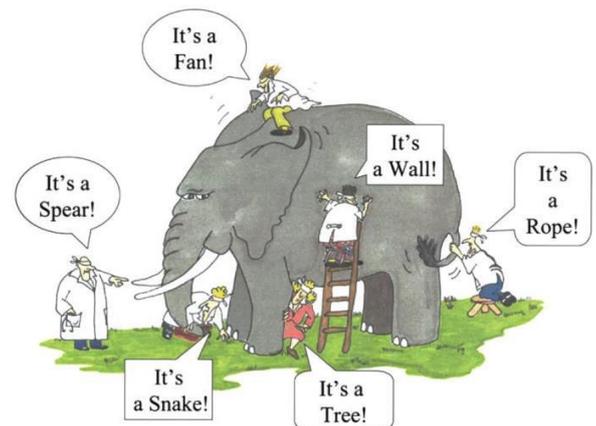
Finally, he highlighted the Biobank's recently published [handgrip strength study](#) which offers a potential means of measuring functionality and the hope that it could be developed as a diagnostic tool.

An elephant? Or perhaps a series of different elephants?

Dr Shepherd was especially upbeat about the recent [CMRC conference](#) in Bristol. He was clearly eager to share all that he learned, but just as clearly biting his tongue as many of the researchers who had spoken are still waiting for their papers to be formally published.

Again, being the true professional that he is, he certainly would not wish to incur their displeasure by spilling any beans in advance....

Prof. Moreau from the University of Montreal used this image (opposite) to illustrate his point that there are a lot of researchers across the world specialising in narrow and specific areas of the M.E. 'elephant'. All coming up with their own theories, but each based on a tiny fragment of the whole picture.



More collaboration is needed – so that we can see what the whole elephant looks like. That is why Dr Shepherd and the ME Association are so keen to bring together people from different disciplines.

Dr Shepherd pointed enthusiastically to the collaboration between Oxford and Newcastle Universities in the metabolomics and [mitochondrial function studies](#) funded by MEA Ramsay Research Fund.

And he is thrilled that Dr Jo Cambridge of University College London is also now [working closely with the Biobank in a study looking for a link](#) between immune system dysfunction and energy production.

But more than one elephant? That’s the cloud to this silver lining...

To make things even more complicated, research is indicating that M.E. – like many other complex illnesses – has subgroups of patients who will react in different ways to particular drugs or treatments. So, as we learn more, it is growing increasingly unlikely that research will produce a *single* treatment or ultimately a *single* cure for this illness.

Important work is now going on that aims to find biomarkers that will define and identify particular subgroups of the M.E. patient community.

Piecing together the jigsaw

M.E. research has brought us great advances in knowledge, but we still are some way from piecing together the jigsaw to see the complete picture. To do that, more research is needed. There’s no escaping this hard fact...

You can’t just produce one positive test result, you need to retest and then test again. This is because what works for one group of samples, might not work again when tested by someone else under different conditions or with different types of laboratory techniques.

And then it might not work for a bigger study with more participants or ‘gold standard’ trial – as was found to be the case with [Rituximab](#).



Dr Shepherd with Jennifer Brea, Countess of Mar and Jessica Taylor-Bearman in Parliament for Unrest (2017)

Only once independent research has produced the same robust and consistent results, can we all move forward to the next stage. So that is why, for example, Dr Shepherd is so keen that [Dr Karl Morten has added metabolomics](#) to his existing mitochondrial dysfunction research to see if it is possible to replicate [Dr Robert Naviaux’s work](#) that holds such promise. We will hear more from Dr Morten in the new year.

Dr Shepherd is also thrilled that we are beginning to bring more experts into M.E. field. For example, at Oxford –Dr James McCullagh who is working with Dr Morten on a [metabolomics](#) study, and at Newcastle – [Cara Tomas’s well received work](#) on muscle energy metabolism.

He also mentioned the valuable work that had been finished, but sadly not yet published, by [Newcastle and Oxford](#) into the validity of the mitochondrial function test that had been developed by Dr Sarah Myhill. He was also looking forward to [Prof. Stephen Todryk and Prof. Julia Newton](#) publishing the results on their immune function investigations.

Another vital element to this piecing of the jigsaw is the [post-mortem work](#) that the Ramsay Research Fund supports at the Addenbrooke’s Hospital in Cambridge. We are the only charity to provide this vital service and we hope one day to have enough funding to build a post-mortem tissue bank.

A number of post-mortems have now taken place in the UK and [some interesting findings](#) have been reported. These include evidence of dorsal root ganglionitis – which probably equates to inflammation in bundles of nerve cells in the nerve roots that transmit sensory information back to the brain via the spinal cord.

The MEA Ramsay Research Fund has invested over £1million in UK M.E. research and still has a key part to play; supporting projects that confirm hypotheses or advancing new ideas. Dr Shepherd specifically asked that I explain here just how closely he works with other medical and research experts, as well as the other trustees at the ME Association, to encourage and promote [new research](#) that advances our understanding.

The more work that is done at this level, the greater our overall knowledge and understanding, and the sooner we shall be able to see that big picture. That is why we are asking for your support for our [Ramsay Research Fund Christmas Appeal](#) – so that we can fund more projects than ever before in 2019!

“How do you eat an elephant? One bite at a time...”

I’m sure that I’m not the only parent to quote this saying to stressed-out children apprehensively facing piles of revision for exams...

And ‘one bite at a time’ is exactly the same approach that we will have to use if we are to bring new drugs and treatments to market.

Again, in my innocence, I blithely assumed that once a research project had got a positive result, it was just a matter of a few short months before a treatment could be devised, tested and introduced for doctors to prescribe. If only that were so!

My trusty dictionary tells me that a ‘trial’ is a formal examination of evidence, or a test of the performance of something.

But it is also something that tests a person’s endurance to the very limit, which is something that our fundraisers relate to only too well as they tackle their physical challenges! Sadly, the trial process for drugs and treatments is similarly hard and tortuous. And it comes with no guarantee of a medal at the finishing line...

Dr Shepherd guided me through the intricacies of the process, explaining that most research projects funded by UK M.E. charities are lab-based and use relatively small numbers of samples from small numbers of patients. These are essentially the first phases of research and are aimed at finding what causes or perpetuates the disease.

As and when a scientist confirms a theory (e.g. that a particular drug could work), then that drug then needs to go forward for a series clinical trials before UK doctors can start treating patients with it. Dr Shepherd mentioned that consultants and specialists might, under certain circumstances, be able to prescribe an unlicensed and speculative form of treatment. However, GPs could risk their licence to practise if they prescribed unlicensed and speculative drugs.



Dr Shepherd with the first GP at the RCGP conference. Impressed with the 2018 MEA clinical and research guide!

In UK, all prescribed drugs need to be recommended for treatment of a specific medical condition by NICE (National Institute for Health and Care Excellence). And NICE won't be 'nice' and recommend that a drug can be prescribed by our GP's until it has been shown to be safe and effective in clinical trials.

Dr Shepherd hopes that NICE's attitude to some possible drug treatments for M.E. might become a little more relaxed when its new guideline is published – but we will have to wait until 2020 to see exactly what it recommends.

The final stage in the clinical trial process (what are termed phase 3 clinical trials) can easily cost in the order of £500,000. This is almost certainly beyond the reach of individual charities in UK. So, we're going to need help with that one – from either drug companies, or the Medical Research Council (MRC).

And funnily enough, Dr Shepherd has already approached major drug companies here in UK and is also talking to the likes of the MRC and laying out the groundwork for when that possibility might arise. He was pleased that the MRC attended and contributed to the Bristol conference.

He tells me that we are working with the CFS/ME Research Collaborative (CMRC) to try and improve the biomedical research funding situation. The [MRC's highlight notice](#) makes it clear that such funding is a high priority to help increase understanding of underlying disease mechanisms and biomarkers of M.E. but we haven't seen any increases in recent years.

But we won't just need funding. We also need to find clinicians who are:

- willing and able to take on the job of diagnosing and managing people with M.E.
- who agree that M.E. is a physical illness.
- who are based in hospitals where there are clinical trial units.
- like the wonderful and sadly recently retired, clinical immunologist Dr Amolak Bansal, who have all the resources of an NHS teaching hospital behind them.



Members of Forward ME with Dr Shepherd and Ewan Dale at RCGP 2018 in Glasgow.

Dr Shepherd recognises the importance of this point and speaks with doctors as often as he is able.

Most recently he played a key role in the M.E. awareness events at the [RCGP Conference in Glasgow](#). His presentation reached over 250 GPs – a full-house – and he and our Scottish Trustee, Ewan Dale, also helped with the Forward ME stand which was visited by many others (photos above).

He also highlighted the encouraging work of some clinical researchers abroad such as [Jose Montoya](#) at Stanford University who was looking at drug treatments, including the use of antiviral drugs that might work on particular subgroups of people with M.E.

Clinical trials take time to perform. "We're probably talking about 5 years at least" from start to finish for a clinical trial of just one drug, Dr Shepherd told me. And there are so many drugs out there that *could* be tried, once we have an accurate picture of which bits of the body are likely to be most responsive to drug treatment.

That's why we have a duty to undertake our research beforehand – as thoroughly and as comprehensively as we can. Because there is little point in wasting valuable time, money and resources or in raising the hopes and expectations of M.E. sufferers unnecessarily.

We're on the right mountain, with Dr Shepherd as our guide...

So, from what I can tell, we are on the right mountain, and are quite a way up it – thanks in no small part to Dr Shepherd's knowledge, enthusiasm, and skills as a guide.

We have confidence in the direction that we are travelling in, but we still have a long way to go.

I met up with one of our fundraisers, Emma Jenkins, after she climbed [Ben Nevis](#) earlier this year with her husband.

She described how, after climbing each hillock, there was another in front. The mountain seemed endless. But I wish I'd kept the voicemail that she left for me at the summit – she was so joyous, so thrilled, and so relieved.



Helen Hyland from the MEA with Emma Jenkins and her husband. Ben Nevis 2018.

We can't see the summit of our M.E. mountain yet. Sometimes the cloud clears for a second or two and gives us a hint of what might be up there. But we've got to go on. We've got to persevere.

We've got to do this to give hope to the thousands of people in UK struggling to live their lives with this horrid illness. We have got to keep striving in the hope that one day we will indeed find a treatment or better still, a cure for M.E.

That is why we are pushing so hard for more funding for research in 2019 and for the [Ramsay Research fund Christmas Appeal](#).

How you can help us to move forward.

I'll leave Dr Shepherd to have the last word...

"Until we have a better understanding of the complex underlying disease mechanisms in M.E., we cannot move forward. The Ramsay Research Fund is closely working with three centres of excellence – at Newcastle, London and Oxford – to further that understanding.

We are also working hard to get new experts into the field. The more research that we can do, the closer we will get to the answers that we are all searching for. I know that this is an expensive time for so many reasons, but please give anything you can spare to support the [Ramsay Research fund Christmas Appeal](#).

One day we will understand M.E. and because of your help, that day will arrive that much sooner. Thank you."



Dr Charles Shepherd

The MEA Ramsay Research Fund Christmas Appeal

If you would like to support our Christmas Appeal, then please:

- Donate [online via our JustGiving](#) page,
- Donate by card over the phone to head office (01280 818964).
- Donate by cheque payable to The ME Association (with a note saying that it is for the Christmas Appeal) to ME Association, 7 Apollo Office Court, Radclive Road, Gawcott, Buckinghamshire, MK18 4DF.

For more information please visit our [Christmas Appeal](#) webpage. And if you have any questions get in touch with Helen Hyland or Head Office.



From us all at the ME Association, we hope you enjoy a safe and comfortable Christmas and more hopeful New Year. Thank you.