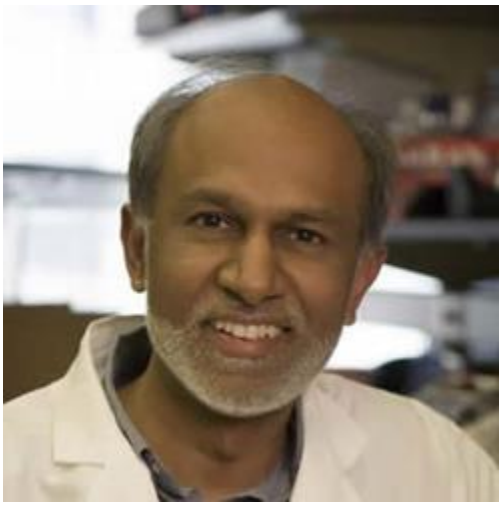
NIH to focus its ‘world-class’ technology and expertise on ME/CFS



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- By Simon McGrath

Categories: All News, Country, Featured news, Medicine, Research, Topics, Uncategorized, United States

On 21 April Dr Avindra Nath gave a Solve ME/CFS Initiative webinar hosted by Dr Zaher Nahle.

The phrase that stood out in Dr Avindra Nath’s description of the NIH ME/CFS study was ‘world-class’. He emphasized the innovative technology the NIH has at its disposal, and its distinguished experts on just about every subject that’s relevant to ME/CFS. Nath mapped out how the study will bring some serious firepower to the study of ME/CFS, particularly to get a better understanding of what’s really going on in the immune system.

Nath also expressed concern that the ongoing level of criticism of the study from patients is putting off good biomedical researchers lending their expertise to the study.

Late last year, Director Dr Francis Collins assembled a team of experts, including Nath, to discuss what the NIH could do to study ME/CFS. The discussion soon focused on the role of the immune system and Collins asked Nath to lead an in-house (intramural) study.

Nath’s credentials make him very well placed to study ME/CFS, with expertise in immunology, viruses, and the brain, but he’s also a clinician: a rare combination of skills in his field of neuroimmunology and infectious diseases. Nath has seen many ME/CFS patients himself, and added that his role running a multiple sclerosis clinic might be relevant as well. Fatigue is often the most disabling symptom in multiple sclerosis, and many patients respond to

immunomodulatory drugs. Nath has already said that if they can identify immune problems in ME/CFS, the final phase of this study would be to test if immunomodulatory drugs can improve the health of ME/CFS patients.

Nath's hypothesis is that, for a substantial subgroup, ME/CFS is triggered by a viral illness that results in immune-mediated brain dysfunction. As he explains, "that brings in our expertise: we have the virology, we have the immunology, and we have the neuroscience." The study focuses on patients who had an infectious onset, which could be bacterial as well as viral.

NIH study aims to find new avenues to explore…

According to Nath, there are basically two ways to run a well-designed study: you can do a few things to a lot of patients, or you can take a few patients and run a wide variety of tests.

The NIH intramural program excels at doing a really deep study of a few patients, he said, while outside research groups were very good at focusing on a relatively few things in a very large group of patients.

The NIH is uniquely well-placed to do a small, exceptionally intense study of patients because of its leading-edge technology and breadth of world-class researchers. It is the researchers' hope that the study will generate new findings that outside researchers can then explore in larger, more focused studies. That, of course, is a case where RFAs and NIH grants will come in.

Three-stage study

This "study" is actually a series of three. Phase one, the focus of Nath's talk, is the deep, deep study of patients that aims to clearly identify abnormalities and biomarkers – ideally, those that play a role in driving the disease rather than simply being markers of it. Phase two aims to check that these findings hold up in a cohort of patients tracked over time. The final phase aims to target those abnormalities with drugs, to see if changing those factors will impact the illness.

Assessing patients, probing fatigue

Phase one of the study starts with a detailed clinical profile of every patient: this includes the usual in-depth history, physical, psychiatric, infectious disease and neurological assessments, and the less common endocrine function, autonomic function, exercise capacity and fatigue testing.

Next, the researchers will systematically probe the physiology of fatigue by measuring function of brain and body both before and after exercise. That's a core part of the design, and never before has a study taken such a comprehensive look at the impact of exercise on patient's biology and functioning.

Brain function will be measured doing both thinking and physical tasks, using fMRI scans to see which parts of the brain are used, how that compares to controls, and how function changes after exercise.

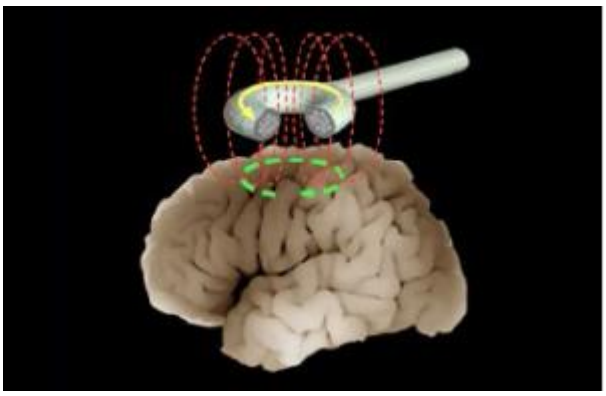

Figure 1: A magnetic coil placed next to the head induces an electric pulse in the brain. Graphic: NIH

For the first time in ME/CFS, researchers will also probe the brain using a technique called transcranial magnetic stimulation (TMS) to stimulate circuits within the brain, to see if those circuits respond as they should.

Also for first time, researchers will study patients in a metabolic chambers that measure how people use energy overall, both at rest and when asleep; this collects a lot of metabolic data, said Nath, and should give information about mitochondrial functioning as well. It will show whether changes in metabolic function occur after exercise.

Nath pointed out that all these technologies – fMRI, TMS and metabolic chambers – were pioneered by the NIH, with world experts on each ready to help with the study. Finally, they will measure autonomic function (yes, more NIH world experts in that field too, said Nath, and they have agreed to help).

Forensic investigation of the immune system

Many studies have implicated the immune system, but none have yet come up with a consistent finding that could explain the disease. Nath thinks the NIH might be able to change that by bringing to bear technology and approaches that simply haven't been used in ME/CFS ever before.

For example, the study takes a unique approach to cytokines and chemokines, the molecular messengers of the immune system. Dr Nath's lab has developed a new system that can detect 1,500 of them, he said. That's an awful lot: by contrast, Drs Lipkin and Hornig measured what was considered a very respectable set of 51 cytokines and chemokines in their headline-grabbing study last year. Detecting such a vast array of the immune messengers should help the NIH home in on the problem – but that's just the start.

Nath said they will be using flow cytometry to measure all the different immune cell types, and their activation status: this has been done before, but the NIH will do it both before and after exercise. They will also use flow cytometry on the cerebrospinal fluid that bathes the brain: another first, and another reason to hope the NIH will find something new and important. It turns out the NIH has a lot of expertise in studying cerebrospinal fluid immune cells and has a wealth of data on other disease populations too, so researchers can see how ME/CFS compares.

This is just the beginning. Nath believes the exceptional cytokine and immune cell profiling work will show where they need to go next. If the data indicates a B-cell mediated disease, he said, "then we will just clone out all the B-cells from these patients." That 'just' covers a whole load of wizardry: there are vast numbers of different B-cells but each in tiny quantities, cloning involves growing each of those different B-cells into a big enough clone to study. That wasn't possible at scale even a few years ago. If the results point to problems with T-cells, they will clone those instead, adapting the study as results emerge.

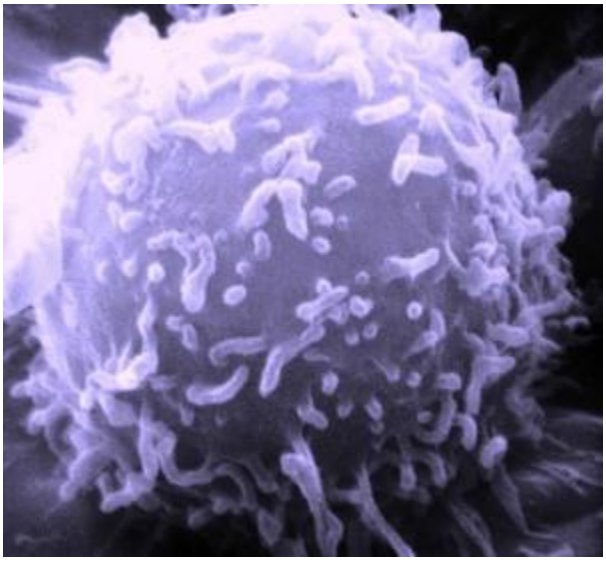

Figure 2: A B-cell, which may play a role in ME/CFS (they are targeted by rituximab therapy). Photo via Wikipedia

Of course, it helps that the NIH's Center for Human Immunology, autoimmunity and inflammation is on hand, which, says Nath, has the largest and best immunology program of any place in the world. The same will apply in other areas too: as clues turns up, the researchers will choose the best approach to pursue next, and there's likely to be a world-class scientist on hand a the NIH who can help. That, of course, doesn't guarantee results, but it's a good start.

There are a load of other things they will test for too, including proteins in the cerebrospinal fluid, autoantibodies, a multitude of viruses, and gut and mouth microbes, which will be sent to Lipkin for analysis.

New approach –growing and studying patient cells in the lab

Nath pioneered a new approach to studying disease in his lab, one he is excited to use in ME/CFS. His lab uses stem cell technology to go from blood cells to just about any other tissue, and in the case of ME/CFS, they will grow neurons. Researchers can test the electrophysiology, and mitochondrial functioning of cells grown in lab dishes, something that you simply couldn't examine in neurons in patients. The team will also test to see if the neurons themselves are normal, but something in the patient's blood has triggered a neuronal problem.

Nath says this is now the go-to technique for all the diseases his lab studies.

Heterogeneity: the challenge of subgroups

A big question with ME/CFS in general, and this study in particular, is 'what happens if not all the patients really have ME/CFS?' Even without the debate over case definition, Nath said that it's an issue for any disease where there are no biomarkers or tests, and diagnosis relies on clinical criteria. That's the case for many neurological diseases, including Parkinson's disease. Inevitably with clinical criteria you'll get heterogeneity, a mixed bag of patients, some of whom don't really have the disease. "But that doesn't actually bother me because as you study those patients you'll find outliers that don't fit into the rest of the group," he said, adding that outliers can be useful.

You can exclude the outliers (say, if a few depressed patients slipped through, he said), or zoom in on them.

For instance, if ten patients form an interesting cluster with the same immune profile, he'll try to understand what identifies those patients, and bring in more patients like that to understand them the cluster. Nath said he had a lot of experience with this kind of problem: some heterogeneity is inevitable, and the clusters that result can provide real insight.

Time to let the NIH get on with it?

This study has become a hot potato, and that's clearly taken Nath, and others at the NIH, by surprise. I doubt many there are used to such sharp and informed criticism from patients. Nath was clearly a little frustrated with the level of continued public criticism from patients, which he feels is now harming the study by putting off researchers he wants to help. One scientist told him "I don't want to have anything to do with it, I've got enough things that I'm doing." Others who typically say yes to Nath haven't got back to him with his request to work on this study.

These NIH studies don't have hierarchical teams where the boss allocates his or her people. Mostly researchers – many of them leaders in their field – get to choose which projects they work on. Only two people will be recruited to work full-time on the study, a nurse and a coordinator: Nath needs most of the rest to agree to help.

These aren't the kind of researchers patients might not want to see on the study: Nath's focus is purely biomedical. He stressed that he was a neurologist who knew nothing about psychology or somatisation, and he wasn't interested, either. He's not trying to pull in people to look at the psychology of ME/CFS.

He cautioned patients to be "a little bit careful as to how critical you become**.** You can end up antagonizing all these people and they are busy doing other things, you can't force people to study your disease."

However, Nath said he was eager to get patient input in a more organized manner. Asked about patient representation, he said the 'extramural folk' were trying to put together a panel of patient representatives and he would be delighted use the same panel for this study. This could help improve relationships with patients going forward, with a clear way for patients to feed in views, preferably before further decisions are made.

Nath also pointed out that he'd answered many emails from patients; and the NIH has developed its ME/CFS website for patients.

Results in two years… or more

Nath said it will take a minimum of two years to get through all the patients and controls – each patient needs to be admitted to hospital for a week, and given how many different diseases the NIH studies there's a lot of competition for those hospital beds. The first controls will be tested this summer, which will also give researchers a chance to fine tune the protocol. Data analysis will

add to the timescale. Then there's publication, and phase two and phase three still to come. This study will run for a good while yet.

Dr Avindra Nath's expertise in neuroimmunology and infectious diseases is a good fit for ME/CFS. That the NIH have him working on Ebola and Zika indicate he's highly-rated; and his publication record is deeply impressive. The study pursues a hypothesis many researchers share: that an initial infection triggers abnormalities in the brain and immune system leading to the symptoms of ME/CFS. Nath's study brings many new techniques to ME/CFS, will bring in top-notch researchers, takes a comprehensive approach from metabolism to immunology to cell culture, and is built around studying the impact of exercise on patients. There is good reason to hope that the NIH, with its unique resources and approach, will find something new and important that will dramatically advance our understanding of ME/CFS.

Note that this isn't a complete summary of Dr Nath's Solve ME/CFS Initiative webinar with Q&A (see transcript with slides or video). More on the NIH study here.

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Tags: biomarker, MECFS, medical research