The heart of the matter? Lipkin's Collaborative probes the impact of exercise

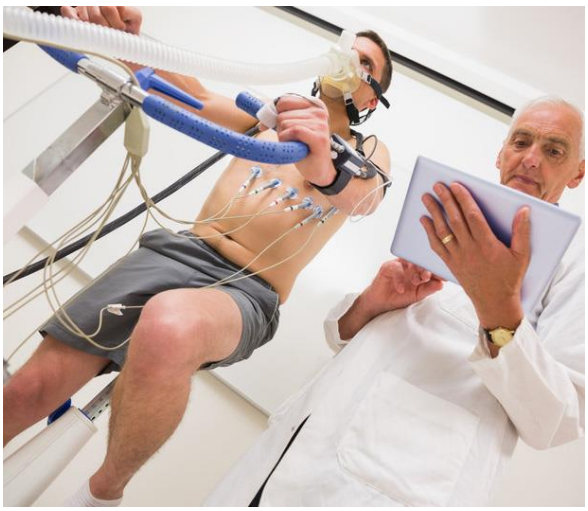
The hallmark symptom of ME/CFS is post-exertional malaise (PEM), a prolonged, grim and disproportionate response to exertion. While Dr W. Ian Lipkin's NIH-funded Collaborative - the Center for Solutions for ME/CFS – is focusing primarily is on how problems in patients' gut microbiomes might drive the disease, his team is also probing deeply what happens when patients exert themselves. Lipkin says that the exertion studies are so important that the Collaborative will devote a third of its research resources to it.

When I spoke to Lipkin about the Collaborative's work, he also said he was very hopeful that there would be real progress for patients within five years. More on this later in the blog.

Exertion studies

The Collaborative has a simple idea for exploring PEM: use two different exertion tests that should provoke symptoms in patients and then see what happens, both to how patients feel and to their biology.

If biological changes, such as those to cytokines, ramp up along with symptoms then it's more likely that the biological changes are directly related to the illness and should give clues as to their role. Any insights into the nature of PEM could lead to a much better understanding of ME/CFS.



Fifty patients and controls will undergo a single maximal exercise test, a sure-fire way to provoke PEM. Patients' symptoms will be measured before the test and then 24 hours, 48 hours and one week after the test. Crucially, researchers will collect blood, saliva and stool (poop) samples on two occasions: before the test, and 24 hours later.

The other, gentler exertion test, called LEAN, simply involves patients leaning against a wall for ten minutes. This test is designed to induce orthostatic intolerance – the development of symptoms when standing upright that ease when lying down – which is a common problem in ME/CFS. Symptoms (including brain fog, tested using a special phone app) will be measured just before the test and at three time-points afterward. Researchers will also check blood pressure and take other clinical measures both before and immediately after the test.

The researchers running the Collaborative's immune study will apply transcriptomics (which examines gene expression) and metabolomics to blood samples from both the exertion tests. And this should reveal any biological changes as symptoms kick off.

Patients and samples

The basis of any good study is to have samples from a large group of robustly diagnosed patients. The Collaborative already has such samples for the microbiome/immune work that was discussed in Part 1 of this blog and is assembling a new cohort of patients and controls for the additional work. This is necessary because many of the patients who provided samples for the earlier projects aren't available for the exertion studies and other work discussed here.

Dr Anthony Komaroff will head the team overseeing this work, and that team will also run the exertion tests. Patients will come from the clinics of expert physicians Drs Susan Levine, Jose Montoya, Dan Peterson and Cindy Bateman – some of the finest ME/CFS clinicians in the US. They will recruit 100 patients and 100 controls.

Dr Dana March, Assistant Professor of Epidemiology at Columbia University, is a key part of the team and their projects, which include mining existing patient data for insights, and creating a new app.

A new bioresource to power future research

With this work the project is also creating a "bioresource" of well-defined patients and of samples taken both before and after exercise. Lipkin says that researchers from both inside and outside the Collaborative can draw on the bioresource to power a new wave of studies.

Lipkin said that the Collaborative itself would like to make more use of the samples: for example, running epigenomics and proteomic profiling of the exertion-study blood samples, and analysing the stool samples, work that would have allowed his team to have the same data on these patients as for the microbiome study. As yet, he doesn't have funds for this work.

The MyME/CFS app

The Collaborative have more in store for this cohort of patients. Working with a tech company, they will create an app for patients that will help both patients and the clinicians to track the illness for an extended period. The app will collect information in real time from patients, covering their symptoms, activities, events in their lives, including other illnesses and any treatments they are trying. This detailed history could help identify what might be causing any setbacks, relapses or even improvements.

Komaroff has said that using technology like this will allow researchers to collect much more comprehensive information much more cheaply than was possible before. Work is already under way, and the team have started by asking patients what they really want from the app.

Mining data for insights

Lipkin has data from several previous studies that all used the same group of patients. The team will combine the data from these studies into one unified database, creating a rich seam of biological, clinical and survey data on a single set of patients. The team will then mine the combined data, looking in particular for patient subtypes and for risk factors.

For example, subtypes might be based on how the illness started, symptom clusters, gender, types of other illness patients have had or how long people have been ill. Risk factors could include previously having a different disease. The idea is that the data will talk.

The team will also bring together and mine data from studies that used the same measures, but not necessarily the same patients. This could also help reveal subtypes and risk factors.

Bringing it all together

One of the most exciting things about this project is the wealth of data the Collaborative will have on every patient they study. For the first group of patients, this means the detailed molecular profiling of the microbiome and the immune system – including antibodies to "self" and to past infections – coupled with rich clinical data. For the second, newly recruited cohort of patients, the Collaborative will have data on their molecular and physiological responses to exertion, along with clinical data, plus the same data on antibodies as the first group of patients – and the data tracking patients' health in relation to a whole collection of factors.

Combining results from such different sources will provide researchers with a deep and rich source of data that will dramatically increase their chances of finding what's going wrong in ME/CFS.

With so much new data to explore, it's possible that Lipkin's group will be able to identify any subtypes of patients, regardless of findings from the data-mining of existing studies.

The crystal ball

I asked Lipkin how he thought things might look at the end of the five-year NIH funding for the Collaborative's research program.

He was bullish about the prospects for significant progress. He made a comparison with the situation with cancer treatment 20 years ago. He believes that in ME/CFS, as with cancer, a group of similar-looking patients will prove to have different causes or triggers for their illness but will share a final common pathway: "ME/CFS". As with cancer, he expects they will find the specific cause of ME/CFS for some groups of patients quite quickly – the low-hanging fruit.

On the other hand, Lipkin believes it may prove much harder to find causes for ME/CFS in other patients – the fruit higher up the tree.

Lipkin is aiming for precision medicine, where doctors try to establish each patient's exact problem so that it can be treated in the most effective way. If for example, the microbiome is abnormal, there are already plausible treatments available, such as probiotics, antibiotics or antivirals that could have a profound impact on illness. Other patients may have abnormalities in immune system or mitochondrial function that will require the development of specific drugs or genetic therapies.

Lipkin said that he hoped that the Collaborative network could be starting clinical trials in three years' time – assuming that results support that next step. He stressed that these trials should be as rigorous as those used for other diseases. To avoid bias in interpretation of results the trials should be blinded so that neither the patient nor the researcher knows whether the patient is receiving a specific treatment. And adverse events – patient harms - should be tracked by a data safety monitoring board.

Lipkin noted that his team and others are already working across the US and internationally to share ideas, expertise, data, samples and other resources. He asked me to assure the community that we have reached an inflection point in the history of ME/CFS research and wanted to specifically thank the community for its support.

In some ways, his programme of research represents a voyage of discovery, and Lipkin's not sure what he'll find. The Collaborative will set off in the most promising directions with the tools and the samples but will change course, if necessary, based on the results, following the evidence to see where it leads.

Whatever the final course taken, the goal remains the same. In a recent NIH briefing-call to patients, Lipkin stated the aim of the Center for Solutions for ME/CFS simply and clearly: to find "real solutions for real people so that we can make it possible for people to become active again."

Read the first part of the blog. **The microbiome hypothesis: Lipkin's collaborative, part 1**

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