

## BBC Radio 4: Inside Science (08.01.26)

**Tom Whipple:** In 1894, as a pandemic known as Russian Flu came to an end, Thomas Downes, a doctor started seeing a different kind of patient. These patients, he said, had a lethargy the like, he had never seen.

“Nature is unnatural to such beings and their very bodily gait and countenance and movements are the outward exponents of the sluggish molecular processes of the weary soul within. This sense of gloom and dejection is a conscious living entity as sad as Hades, where joy and tranquillity and peace and love are unknown. “

In 1920, in the aftermath of another virus this time called Spanish flu, there was famine in East Africa. It wasn't blamed on crop failure, but by a failure of the people to get the crops out of the ground, they were exhausted.

Today after another pandemic, millions around the world complain of similar problems. Is the thing that we call Long Covid unique to COVID, or is it just an instance of something more general? Extreme post viral lethargy for those suffering from ME often blamed on infection. There was hope that research into Long Covid might aid research into their illness.

Now, a major research effort is looking to use deep sequencing to understand at a metabolic and genetic level the immunological parallels between the two. The ME Association has awarded 1.1 million pounds to scientists at Imperial College, and Danny Altmann is the virologist who co-leads the program.

**Prof Danny Altmann:** Across the two conditions about a thousand people get recruited and, as you expect for an immunologist, that sort of biggie is that they give us a blood sample and we analyse immune system cells, white blood cells. They also get asked if they're prepared to give us a stool sample, a poo sample, and they also give us a mouth swab. So, the kind of things we do with that is to kind of interrogate the key hypotheses about possible shared pathways.

So, if we start with the, with the poo sample, there's an idea out there that one of the things that happens in these post-viral conditions is that there's disturbance of the gut microbiota. And that you shift bacterial species and shift over to ones that are, that are making the wrong kind of mediators, the wrong kind of short chain fatty acids, and that they affect regulation of the immune system.

So, we'll be doing a ton of work sequencing genes for bacteria and analysing the things that they make and looking for common pathways there and how they feed into the immune system. We're also very keen on the idea that one of the things that happens as a consequence of a viral infection is that you trigger autoimmunity.

So, we'll be using really fancy techniques to try and probe form, if you like, repertoires of antibodies and cells that recognise self-tissues and could be mediating in front of autoimmune disease, underpinning these things.

**Tom Whipple:** Why are we researching these two conditions together?

**Prof Danny Altmann:** Well, you know, we called this new project and this new proposal, Rosetta Stone, for obvious reasons in terms of the ability you know, one language to decode the other language. Because as time went by over the last five years of working on Long Covid, I think we realized, and I certainly realised that we were to some extent reinventing the wheel and finding things out that people had talked about in ME for years before and felt they hadn't been listened to about.

I think the point we've come to in general in thinking about Long Covid, is that what we're talking about here, a specific example of a virus, in this case, SARS-CoV-2, that causes long-term persistent symptoms that go on long after the acute infection. Which is similar to many other examples that have been around, that we've known about for years, and maybe the one to illuminate all the others, but we're thinking about a kind of umbrella term for lots of these persistent viral conditions.

**Tom Whipple:** The big issue amongst people with ME has been diagnosis, with Long Covid have we found ways of finding in the body a signal of the condition?

**Prof Danny Altmann:** So, I'm hesitating aren't it. So, kind of, yes. Okay, so obviously, you know, the word that people use in this connection is biomarkers.

And we need biomarkers because we need diagnostic tests for everything, don't we? So, if you were to do a, a search for how many peer reviewed publications they've been proposing agreed biomarkers for Long Covid. You'd come up with a number of several hundred, and some of them I think are, you know, are good biomarkers look solid to me. But if you can hear hesitation in my voice, it's 'cause it's usually in immunology, we failed to achieve consensus, to do well enough at knocking heads together and getting the answer rather than loads of answers.

And I think the way that I feel, and lots of people feel. In the field at the moment is we need to do that. That knocking of heads together, we need to kind of organise the international workshop where we pull together a lot of samples from thousands and thousands of people Long Covid. To say, you know, never mind the 800 answers that got published in the medical literature, find us four or five answers that could be a test in every GP surgery in the country. And I think that's the kind of, you know, transition point we need that we're almost at.

**Tom Whipple:** If we had that, would there then be an overlap with ME? What would it mean for people with ME if there was a blood test you could do?

**Prof Danny Altman:** You know, there's no guarantee that the perfect Long Covid test has to be the perfect ME test. But you know, obviously the whole kind of kind of rationale for this new project that we are doing is that there is enormous overlap, and indeed, you know, the majority of the people who have Long Covid would meet the criteria for ME.

So, you could almost think of Long Covid as being a specific case of ME where we just happen to know the virus that's triggered it. Imagine if there was a

laboratory test that you could take, that you could order that came back yes or no, and you know it got you sent to the appropriate clinic. Yeah, that would be transformative.

**Tom Whipple:** Is that realistically possible? Isn't there a problem that things like Long Covid are, by their own very definition, poorly defined, that we've got people who have these really debilitating, persistent long-term symptoms, but we've also got people grouped in it who are simply taking longer to recover from an infection for whatever reason?

**Prof Danny Altmann:** No, I don't really buy into that. So, one of the sort of underpinnings of your question is that it's a diverse condition. Yeah. It's hard to pin down because it's heterogeneous, because the elderly man from the first wave of the COVID pandemic, who's still got brain fog looks so different to the 16-year-old from the omicron wave who's got gastro symptoms.

And yet I think one of the things that both ME and Long Covid have suffered from is being multi-system complex diseases where it's easy for people to throw up their hands and say, well, they're too complex, how can this happen, how can this be a thing? And the answer is, you know, in medicine we deal with multisystem complex diseases all the time, don't we? It's just a matter of the will to grapple with them.

If you'd never heard before of lupus, you'd say, what are you talking about? You know, how can there be this kind of strange nebulous disease that gives you a face rash and CNS symptoms and respiratory symptoms and renal symptoms and on and on, and yet, you know, there is a disease like that it's called Lupus, And it's caused by a very specific mechanism. So, you know, we are on the trail of the specific mechanism or mechanisms that drive these processes in Long Covid and ME.

**Tom Whipple:** Thank you very much Danny, and good luck with finding out what's going on.

That was Professor Danny Altman from Imperial College London. You are listening to Inside Science with me, Tom Whipple.