



An appeal for funding for a major research project that may at last unlock the causes of Chronic Fatigue Syndrome/ME

Chronic Fatigue Syndrome or ME as it is sometimes called devastates the lives of those it afflicts. For many years there has been little understanding of why the symptoms arise, and even less hope of a cure. But recent developments in genetic research are changing all this. The CFS Research Foundation is now funding an important three-year study to identify activated genes that are likely to be involved in the cause and symptoms of CFS/ME.

Background

Following initiatives in the USA and parallel activity in the UK there is now an internationally accepted research definition for CFS/ME. But there has been no laboratory test that can be used to support the diagnosis.

There are clinical studies that indicate that CFS/ME can follow infections, such as glandular fever, enterovirus infection, viral aseptic meningitis or Q fever, even though by standard laboratory tests the active infection is past. It is clear that CFS/ME is caused by many different viruses, but there are also many cases in which there is no history suggesting an infection.

Recent research

The CFS Research Foundation was launched in 1993 to stimulate and fund research into CFS/ME – a disease which was almost totally neglected by doctors and scientists. Since then the Foundation has funded several studies working on different aspects of the problem. Dr Russell Lane took muscle biopsies from CFS/ME patients at his neurological clinic in London. He carefully separated those who had any form of psychological problem. Some showed increased lactic acid production on exercise making the blood more acidic and causing muscle pain and fatigue; this group seemed to be largely distinct from the group with psychological problems. Professor Len Archard and his colleagues, using sophisticated scientific techniques, found evidence of enterovirus genes in the muscle of some patients. (Enteroviruses cause many respiratory and bowel infections especially in the summer; polio viruses belong to this group.) Furthermore he confirmed this by using a different technique and showed that the virus was related to the enterovirus



The Right Honourable The Lord Bingham of Cornhill, Senior Law Lord

"Those of us who know anyone with CFS/ME are only too aware of the personal suffering it brings and the way it may destroy family life, ruin careers and bring untold misery.

This is no trivial illness. Patients suffer overwhelming exhaustion of both muscle and mind, 'flu'-like symptoms, joint pain, muscle pain, loss of short-term memory, loss of concentration, gastro-intestinal troubles, migraine and insomnia. Its devastating symptoms affect those who have been very active, professional people whose careers are suddenly ended, and children and young people who are unable to complete their education either at school or university. Old people, too, suffer, many of them having endured the illness for decades. While some people are able to enjoy a reasonable quality of life, thousands are housebound or bed-bound for months or even for years. There is, at present, no cure.

Doctors and scientists at the CFS Research Foundation, all pre-eminent in their fields, have for ten years been guiding research of the highest scientific standard to unravel the mysteries of this baffling illness. We are now undertaking an ambitious project to compare the genes of people with CFS/ME and those of normal healthy people.

We believe that this study is of profound importance. It is already making good progress, but it is essential that the scientists should be enabled to complete their work."

Lord Bingham



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Dr David Tyrrell FRS,
Chairman of the Research Committee,

"Now is the right time to start to probe this illness by the new genomic methods. I commend the teams with the expertise – and courage – to do this and wish them every success.

The key steps in the project are as follows:

Blood is taken from patients in the clinic and from others who are bed-bound or housebound. In this way samples from those who are not so severely affected and those who are very ill indeed are examined. For comparison there is a control group of healthy people recruited from the local blood transfusion service who are matched by age, sex and geographical location. White blood cells are obtained and then transported to Imperial College London where the RNA is extracted. The next stage is to use microarrays to detect persistent infections. The scientists work with an American firm, Nimblegen Inc, who are expert in this field. The RNA samples are sent to their laboratories in the USA and Iceland where they are tested by a process known as 'microarray analysis'. This determines the presence or absence of RNA of each of 10,000 human genes, analysed in comparison with results from normal people. This will reveal the genes associated with CFS/ME.

The results files are then returned to London to be studied and analysed by Drs Kerr and Kaushik in consultation with Dr Tim Harrison of the Royal Free and University College Medical School, London and Dr Paul Kellam of University College London. The results on 25 new patients show that several dozen genes are activated. At least 5 might form the base of a specific diagnostic test; others will indicate what produces fatigue and other symptoms – and hopefully different sorts of CFS/ME. So we need to start testing larger numbers of patients and gene products to expand and confirm the results so far. In the process we should find new possibilities and targets for treatment."

Coxsackie B3. In his latest collaboration with Dr Lane they have shown that there is an association between detecting part of the virus which provides the viral genetic code (the nucleic acid) and an abnormal result on the exercise test. There was an entirely independent study in Glasgow in which enterovirus nucleic acid was detected in the blood of locally recruited CFS/ME patients with similar results. The results were published in the Journal of General Virology. Using a slightly different approach Dr Jonathan Kerr of Imperial College London, has followed up a group of patients shown by laboratory tests to have been infected with another common virus, the parvovirus B19. A number complained of continuing fatigue and 13% of them had the symptoms of CFS/ME.

When a person is attacked by a virus some genes become very active while others shut down.

The overactive genes produce chemicals which cause the symptoms of the illness. The Foundation funded a project to look for evidence of some genes becoming more active in patients with CFS/ME. The work was done by Dr R Powell firstly under Professor J Almond at Reading and then under Professor S Holgate in Southampton where the patients and control subjects were recruited. White blood cells from about half a dozen patients and a few matched normal subjects yielded evidence that there were several genes in the patients which became more active but remained normal in the control group. Another study showed that one is a known gene, but others can be located in other specific regions in the human genome although the genes involved and their functions are as yet unknown. A paper has been accepted for publication.

Taking the research to the next stage

In the light of our recent research, current developments into gene research and the rapid advances in sophisticated scientific technology it was decided that it was now possible to study the basis of the disease by examining the genes of patients. We already had evidence that several of the patients' genes might be activated and be involved in the production of chemicals in the immune system thus producing the general symptoms of CFS/ME.

The Research Committee decided that it was vital that these studies should be followed by a multi-centre study. It is now possible with microarrays to show which genes are activated across a wide range in white blood cells.

The strict criteria established for the new research

The Research Committee decided that several clear criteria were needed for the work to go forward successfully:

A broad pool of patients

It would be essential to have material from the widest possible number of well-documented patients and control comparison groups matched for age and gender.

The patients should

- fulfil the internationally accepted "Fukuda" criteria and be followed up
- not have other possibly confusing conditions such as major depression, muscle disuse after injury or paralysis, other chronic neurological illnesses

The control groups should

- be apparently healthy but otherwise matched to the patients

Different geographical areas

The patients and the control groups should come from several different areas and from independent clinics.

Searching for pathogens and viruses

Several approaches are being used to search for evidence of the presence of nucleic acid of viruses and other pathogens for which probes are now available.

How unlocking the genes may bring a major advance

A specific programme of research using state-of-the-art microarrays in the laboratories and rigorous international standards is now underway and the results of the first phase have been produced. Using 25 patients it was found that 20-50 genes were especially affected and 5 of these were most consistently altered. It will now be possible to make a laboratory diagnostic test, to recognise different sorts of CFS/ME caused by different infections, to expand our range of tests for viruses which can be treated and to use microarrays to detect persistent infections. We must understand the mechanisms of the illness.

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Dr Kerr taking blood for analysis from a bed-bound patient

To do this we will analyse what these genes seem to be doing and how they are changing the functions of the nervous, immune, hormonal and other systems.

When we can identify the products which the genes are making that are important parts of the mechanisms of the illness we will seek drugs to control them. Clinical trials will be set up and we will need hundreds of volunteer patients for this. We have ethical permission for this work.

Now, at last, we have the tools to examine the basis of this disease. We have every hope that this will lead us to drugs that will control the symptoms or bring about a cure. The study will cost £352,239.50 but the Foundation felt convinced that it should meet this challenge. We have covered the costs of phase one, but we still need £237,058 to complete this study. So much hope is invested in it. We appeal to all to make it possible for the hope to be translated into reality.

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