

Chapter 3

What Causes M.E.?

I - Virus and Muscle Research

To give you a flavour of the current ideas about what causes M.E. and the Chronic Fatigue Syndrome, I can do no better than to quote directly the theories of three researchers, each of whom has seen and investigated many hundreds of patients:

Post-viral fatigue syndrome is a metabolic disorder, caused by persistent virus infection and associated with defective immunoregulation.

(Prof P. O. Behan, 1985)

The condition (M.E.) appears to be a rare complication, mainly in non-immune adults, of a widespread often asymptomatic childhood infection. The group of viruses most consistently associated with M.E. are the non-polio enteroviruses - including Coxsackie and Echoviruses.

When the host immune response is ineffective, viral parasitism leads to mitochondrial damage with resultant energy deficits at cellular level.

(Dr E. Dowsett, 1990)

It is presumed that CFIDS (CFS) is a cytokine-mediated illness, virally induced, in genetically susceptible individuals. [CFIDS=Chronic fatigue and Immune Dysfunction Syndrome, a term for CFS also used in the USA.]

(Dr Jay Goldstein, 1990)

Research has been done into various aspects of M.E., carried out in differing medical specialities:

Virology, and effects of viruses in the body

Muscle abnormalities

Immunology

Red blood cell abnormalities

Neurology, brain involvement

Psychology, psychiatry

Viruses and M.E.

The Case for Enteroviruses

In a small town on the Hudson River in New York State in the late 1940s, a new virus was isolated from children with a disease that resembled poliomyelitis. The virus was named Coxsackie, after the town. It is now known that Coxsackie viruses are members of a group called *enteroviruses*, which include polioviruses and live in the human intestine. Enteroviruses can affect many tissues, but have a particular affinity for the central nervous system and muscles.

In two outbreaks of M.E. in Scotland in 1983, there were significant numbers of patients who had higher levels of antibodies to Coxsackie B virus than were found in the general population.

In a further report of patients with symptoms of M.E. in a west Scotland general practice (1984), nearly half had high Coxsackie B antibody levels. In this same practice, 55 per cent of those with Coxsackie infection were still ill after one year, nearly all having persistently high antibody levels. So it was probable that Coxsackie B virus was responsible for several outbreaks of an M.E.-like illness in Scotland.

The most comprehensive summary of the role of enterovirus infection in M.E. can be found in the paper: 'Myalgic encephalomyelitis - a persistent enteroviral infection?' (Dowsett, 1990)

The human enterovirus family comprises about 70 species, including: polioviruses, Coxsackie A and B, echoviruses, hepatitis A and B, sub-groups of these species, and others. Records exist of enterovirus disease going back to 2000 BC.

Now that a polio vaccine has reduced the incidence of paralytic polio, the non-polio enteroviruses are becoming more important in causing human disease. History has shown that enteroviruses have a great capacity to start new syndromes and new epidemics.

Enteroviruses are known to cause many clinical conditions; examples of enteroviral illnesses are:

Respiratory infections

Gastroenteritis

Hepatitis

Meningitis and encephalitis

Poliomyelitis

Bornholm's disease - (severe chest pain due to involvement of muscles between the ribs)

Myocarditis and pericarditis

Hand, foot and mouth disease, and other skin conditions

Conjunctivitis

Pancreatitis and juvenile onset diabetes, and

Myalgic Encephalomyelitis

Enteroviruses are known to affect muscle and nerve particularly. The two main tissues affected in M.E. are muscle and nerve; enteroviruses are said to be 'myotropic and neurotropic':

Enteroviruses are spread from the faeces of those infected, via sewage, rivers, estuaries, beaches and agriculture, to reinfect humans in drinking water and food. They are easily picked up on beach and water holidays; by hospital workers from bedpans and other equipment; by those who work with young children who frequently harbour enteroviruses without signs of illness - and land and water workers. Most enteroviral infections do not cause any obvious illness. Enteroviruses are not killed in the process

of 'treating' sewage before it enters the sea.

In several outbreaks of M.E., patients were initially thought to have polio (e.g. Los Angeles 1934, Iceland 1948), and health authorities thought a polio epidemic had started, until it became clear that the illness, although resembling poliomyelitis, had some different features. One aspect in which M.E. behaved like polio was that *those who were most physically active when they contracted the infection were most likely to develop muscle weakness.*

In a follow-up study of M.E. cases from a Glasgow college (Durdell, 1989), out of the 31 patients, 12 had been runners pre-illness, whereas only 2 of the 25 healthy controls were runners.

Evidence that enteroviruses are present in a sizable number of M.E. patients resulted from the work of Professor James Mowbray and his colleagues at St Mary's Medical School, London (Mowbray, 1988).

It is difficult to detect virus in the stools because it is bound with antibody, so a method was devised which would detect enterovirus-group-protein in the blood. This protein, called VP1 polypeptide, is common to all members of the enterovirus family. VP1 was detected in the blood of 51 per cent of the tested M.E. patients.

This VP1 test has since been carried out on many more patients with clinical features of M.E., and is positive in about 60 per cent of the cases. If positive, it simply means that there is active enterovirus in the body, but does not identify which one, because the virus protein is common to all of them.

However, the test is also positive in a number of healthy people, and reflects the amount of that enteroviral infection in a community at any time. Enteroviral infections are extremely common, and frequently asymptomatic. The VP1 test, though useful in giving supporting evidence to the diagnosis of M.E. if consistently positive over a period of months, is not now included in routine tests on a patient suspected of having M.E. - it is too non-specific. What distinguishes those with M.E. from others carrying enterovirus is their *abnormal response* to the virus.

The Iceland Research - Akureyri, 40 Years Later

(Hyde and Bergman, 1991)

In Iceland in 1948, the outbreak of an illness that resembled polio but was epidemic myalgic encephalomyelitis, was centred around a small community at Akureyri. Dr B. M. Hyde from Canada has studied some people who fell ill during the 1948 outbreak and are still alive.

Ten people, now aged between 58 and 84, were interviewed, examined and had blood tests performed. Only two out of the ten had made a complete recovery, even after 40

years. They had all had features typical of myalgic encephalomyelitis when they were ill. One had fallen ill in 1955, the others in 1948. Records indicated that the disease became endemic after the 1948 outbreak, so sporadic cases would have continued for years.

Eight out of the ten had a positive enterovirus VP1 test; the two who were negative were the two who had made a complete recovery. Those people who had not made a complete recovery all had some degree of chronic handicap, although they all thought they had made a good recovery. On psychological assessment, none of the ten showed any signs of neurosis or hysteria; they had all achieved satisfying lives or careers in spite of varying levels of disability.

This evidence points to a persistent virus being involved in M.E. Here in Iceland were people who had fallen ill 40 years ago, who all conformed to the features of M.E. syndrome; after 40 years, eight out of ten still had enterovirus in their blood, also persisting disabilities, yet had successfully overcome their handicaps of chronic illness.

Effects of Enteroviruses in the Body

Enteroviruses are known to infect muscle, including heart muscle, the nerves and the brain. They may also infect endocrine glands (e.g. the pancreas, leading to diabetes). Enterovirus RNA (ribonucleic acid) has been identified in muscle cells of M.E. patients. Certain strains may affect the heart, others the brain.

Myocarditis and other cardiac problems, e.g. pericarditis, occur in up to 30 per cent patients with M.E., depending on whether the virus is a cardiogenic strain. This condition may persist long after recovery from the initial infection, in the form of auto-immune myocarditis. The connection between enteroviruses and cardiac disease has been documented for over 30 years.

(Personal communication from Dr E. Dowsett)

The conducting tissue may also be affected, causing irregular heartbeat.

Brain Findings in M.E. Patients

Enterovirus can infect brain tissue. Dr J. Richardson, a GP from Newcastle, recovered brains from three M.E. patients who committed suicide. Prof. J. Mowbray was able to demonstrate enteroviral protein in the cortex of each brain. Using a dye that was specific for enterovirus, staining was observed around small blood vessels, and in glial (nerve) cells. Each patient had been ill for at least two years with an illness typical of post-viral onset M.E. Control brain specimens were entirely free of enterovirus in both the brain and bloodstream. In at least one victim, there was a high blood level of antibody to Cocksackie B, and a positive VP1. [This information comes from a presentation made by Dr Richardson at a symposium on M.E., June 1989, London].

Arthropathy in M.E.

Pain with or without swelling of joints is a well recognised complication of M.E. It may be caused in several ways:

A direct viral infection (as in rubella). Enteroviruses have been isolated from joints of M.E. patients.

Immune complexes (found in 60 per cent of the patients in one survey) may settle in joints and cause symptoms of inflammation.

People with a genetic tendency to get arthritis will relapse if they get a viral infection (e.g. rheumatoid arthritis, which is not caused by M.E., flares up with a virus.)

(Personal communication from Dr E. Dowsett)

The Epstein Barr Virus

Chronic fatigue syndrome was known as Chronic Epstein Barr Virus disease (CEBV) ,in the USA until recently. The EB virus is a member of the herpes family, a different family from enteroviruses. Herpes viruses are 'DNA viruses', while enteroviruses are 'RNA viruses' DNA and RNA being the two types of molecules which carry the genetic codes for reproduction. EB virus is best known for causing infectious mononucleosis, known (incorrectly) as glandular fever in the UK.

EB viral DNA has been found in 20 per cent of the patients in Dr Archard's muscle study which detected enterovirus RNA, but not in the same muscle biopsy specimens.

Glandular fever is well known for the prolonged debility that persists for months after the acute infection. Most people have been infected with the EB virus by the age of 30, usually with few symptoms; only in a few is the infection severe enough to cause glandular fever. If you look for evidence of past EB infection, you will find it in about 95 per cent of people, with or without M.E.

Testing for active infection with EB virus requires special tests. If these tests indicate an active, present EB virus infection in someone with symptoms of M.E., what has probably happened is that a latent EB virus that has hidden in some body cells for many years has become reactivated, causing active or persistent infection. The EB virus can hide in surface cells of the nose or throat, and in B lymphocytes for years. Depression of the immune system (maybe from another virus) allows it to flare up. -

Two researchers, Prof. J. Mowbray (London) and Prof. C. Murdoch (New Zealand) found 20 per cent and 19 per cent (respectively) blood samples positive for active EB virus from patients with M.E. It is possible that other viruses which can remain latent in the body may be reactivated, and appear to trigger M.E.

A newly identified virus, *HHV-6 - human herpes virus 6* has been considered as being involved in M.E. However, researchers in Australia (Wakefield, 1988) found no difference in incidence of HHV-6 between M.E. patients and healthy controls. By one year of age, about 60 per cent of children have antibodies to HHV-6, showing that it is very common and acquired early in life.

However, Dr Josephs and others (1991) have found raised antibody titres to HHV-6 in six out of seven patients with CFS. Cell cultures produced HHV-6 DNA in three of the patients. The authors suggest that HHV-6 may be contributory to the pathogenesis of CFS. However, it may represent a reactivated virus, and not be the main cause.

Another proposed culprit is a newly discovered retrovirus. Dr Elaine DeFreitas of Philadelphia (1990) presented a paper at a congress of neuropathology in Japan. She told how 23 out of 30 (77 per cent) blood samples from CFS patients contained virus particles that resembled those of HTLV 1 and HTLV 2 (retroviruses). The viral particles were detected using polymerase chain reaction. In a separate study, antibodies to HTLV 1 and 2 were found in 50 per cent of the blood samples from these 30 patients. This discovery has not so far been repeated by other researchers, and at present the role of retroviruses in chronic fatigue syndromes is unknown.

A Persistent Viral Fatigue Syndrome?

It now seems possible, certainly in M.E. people with enterovirus, that part of the virus is persisting inside cells, and is interfering with the cells' functions. This is indeed a feature of *persistent virus infections*, which are recognised increasingly as being involved in several chronic illnesses of unknown cause. In acute viral infections which clear up, there is a reaction by the body's defence system; this results in the death of cells that are infected by the virus, and prevents the virus from infecting other cells. Therefore the virus, which can only replicate inside a living cell, stops reproducing and dies out.

However, certain viruses are known for their ability to survive in the human and cause persistent infection.

Dr M. Oldstone (1989) wrote this about persistent viral infections:

Such viruses do not kill the cells, and do not elicit an effective immune response. These tactics enable the viruses to establish a long-term presence within cells, where they can have a subtle and persistent effect - by altering the specialized function of the cell, such as the production or secretion of a hormone. Such 'luxury functions' are not essential to the cell's survival, but may be vital to the health of the organism (e.g. a human). It is likely that immune, nervous and endocrine systems are primarily involved.

M.E. seems to be a persistent virus infection. Other diseases, such as diabetes, Parkinson's disease and schizophrenia, will probably turn out to be caused by persistent virus infections.

In M.E., a virus is probably affecting the special function of brain cells, and indeed many other organs of the body. Some endocrine functions may be affected, such as the pituitary gland, thyroid gland, the adrenal glands (which produce hormones of vital

importance in the body's reaction to stress and infection), or ovaries. The pancreas may be involved in some viral infections; this can lead to poor digestion of food, and also to diabetes. There is no part of the body which is never affected by a widespread, persistent virus infection.

A persistent virus would also continually stimulate some degree of immune response. This response is not great enough to destroy the virus, but has two main effects:

- a) The constant production of cytokines, the chemical weapons made by white cells as part of an immune response. Interleukin 2 (a cytokine) when tried as treatment for cancer patients, caused such unpleasant symptoms - emotional lability, fatigue, muscle pains, and 'flu'-like feelings - that the trial was abandoned. Interferon had similar unpleasant effects when tested on patients with chronic liver infection.
- b) The other effect of an abnormal ongoing immune response (to the persistent virus) is allergic reactions (see Chapter 14). Multiple allergies are common in M.E. - 'The patients' medical histories reveal one striking finding: a high frequency of atopic or allergic illness - up to 70 per cent' (Komaroff and Buchwald 1991).

The question is often asked: is someone with M.E. or CFS infectious to those around them? The viruses that may cause M.E. are carried by a large percentage of the population, in the throat, nose or in the gut, without causing any ill health. It does not seem that people with M.E. are any more likely to spread these common bugs about than the rest of the population is.

It is estimated that roughly one in four of M.E. patients has a close relative or work colleague with the illness. In the case of more than one member of a family being affected, there may be factors other than the virus to consider, such as an inherited predisposition to the illness. The infectiousness of M.E. and other chronic fatigue syndromes is not yet clearly understood. At the present time, some physicians in the USA recommend caution to patients - this includes advice to people with M.E. or CFS not to be blood donors.

So, assuming that a variety of viruses, and indeed other infections and even immunizations, trigger off M.E., what other factors are involved? Why is it that a number of people in a community can be infected with something - say an enterovirus, which seems the most likely virus where M.E. occurs in 'outbreaks' - but only a few develop the M.E. syndrome? And how can one explain the origin of typical M.E. in a person with no obvious infection at the onset? These patients, who report a gradual loss of health and onset of fatigue and end up with classical M.E. syndrome, present the greatest challenge for diagnosis and for understanding how their illness came about. It is likely that one of the main factors which determines whether you get M.E. is the efficiency of your immune system (see Chapter 4).

Muscle Studies

Dr L. Archard (1988) examined muscle biopsies from 96 patients with PVFS; using a special technique, he found enterovirus-specific RNA in 20 cases. It was not present in any of the healthy controls. The percentage positive for enterovirus may be an underestimate, because a biopsy specimen may not always include a sample of muscle affected by virus.

Prof. P. O. Behan and colleagues, Glasgow (1991) recently published important research. Using a new technique (Polymerase Chain Reaction) they identified enterovirus RNA in 53 per cent of the biopsies of 50 patients with typical features of post-viral fatigue syndrome. In 41 controls, enterovirus RNA was positive in 15 per cent (all positives were in patients undergoing surgery for cancer).

The enterovirus found by this PCR method was studied further by sequencing the molecules of its RNA.

This revealed that the virus was a possible variant of poliomyelitis and most closely resembled polio vaccine. Further studies have shown that this particular sequence resembled a cell protein *calsequestrin*, which is involved in calcium metabolism.

(Behan, 1991, British Medical Bulletin, p. 808)

These findings may be important in studying cell malfunction in M.E. Further research on this is going on at present.

Dr Archard (1990) published further work on enterovirus RNA which showed a mechanism that explains why enterovirus becomes persistent in a small minority of people:

Muscle biopsies from PVFS patients that were positive for enteroviral RNA were used. The production of virus RNA in these samples was compared with RNA production in cultured cells infected in the laboratory. The results showed that there is a defect in the way the enterovirus in the M.E.-affected muscles reproduces itself. The normal virus 'identification code' therefore may not be present, and the virus does not multiply. The immune system may not recognize the defective virus RNA, does not destroy it, nor produces an inflammatory response.

The same phenomenon is seen in dilated cardiomyopathy (a serious condition which may necessitate a heart transplant), a presumed progression from a viral myocarditis, and so may be a general mechanism of enteroviral persistence.

Mitochondrial Abnormalities

Dr D. Doyle (1991) described a study of 130 patients whose muscle biopsies were examined by electron microscopy. Mitochondria are tubular structures present in every cell nucleus. They are the cells' power stations, where energy is produced from a metabolic process using oxygen and glucose. Abnormalities were identified in functions, energy storage mechanisms, and the appearance of mitochondria. Samples were studied for presence of virus particles, and positivity for the virus correlated with electron

microscopic abnormalities of mitochondria.

In another study (Behan et al., 1991), examination of muscle biopsies from 50 patients showed abnormalities of mitochondria in 80 per cent, and in none of the 50 controls.

It is tempting to speculate that a persistent virus might interfere with mitochondrial DNA, leading to muscle fatigue. Similar damage to the central nervous system might account for the psychiatric features, described in this syndrome and for the hypothalamic dysfunction which we have recently identified.

Electromyography (EMG)

Jamal and Hansen (1985, 1989) carried out single-fibre EMG on 40 patients. Abnormally high 'jitter values' (measurements of muscle fibre irritability) were recorded in 70 per cent of the patients.

In a further study, single-fibre EMG was carried out on 10 patients with PVFS. All the patients showed abnormal jitter values. Muscle fibre density was normal in each case.

A muscle membrane disorder, probably arising from defective myogenic enzymes, is the likely mechanism for the fatigue and the EMG abnormalities. This muscle membrane defect may be due to the effects of a persistent viral infection.

Muscle biopsies were carried out on these 10 patients. All showed some abnormal findings in their muscle fibres, and in the mitochondria of all patients, which suggested a problem with cell energy metabolism.

Four of these patients had nuclear magnetic resonance (NMR) studies carried out (see below): all had positive results.

All these findings confirm the organic nature of the disease.

Nuclear Magnetic Resonance (NMR)

Arnold, Radda and Bore (1984, 1985) have demonstrated *early excessive acidosis* (excess lactic acid in muscle tissue) in the exercised muscles of patients with post-viral fatigue syndrome, using Nuclear Magnetic Resonance (a method for assessing biochemical changes in tissues). Muscles of patients were tested during exercise, and excess lactic acid was produced abnormally early. The conclusion drawn was that there was a defect in the balance between the two kinds of energy production.

In M.E.-affected muscle there may be too much of the anaerobic energy pathway (which uses glucose) compared to the aerobic route (which uses oxygen), causing excess lactic acid production. This could account for the muscle pain and severe malaise after exercise that accompanies M.E.

Electron microscopy had already shown an increase in size and number of Type II muscle

fibres, (Jamal, above) which are the muscle fibres that use the anaerobic pathway, releasing lactic acid.

Abnormal Protein Synthesis in M.E. Muscle

Prof. Peters (1991) examined muscle biopsies from M.E. patients for RNA, DNA, and protein content. There was a significant 17 per cent decrease in total RNA per cell. Further studies demonstrated a decrease in muscle protein synthesis in M.E. patients (Pacey, 1988). A lessened ability of muscle to repair itself might contribute to the rapid fatigability of M.E. muscles.

At Biolab in London, Drs S. Davies and J. Howard have developed a test of muscle function which uses fine heat sensors to record muscle activity - a *myothennogram*. In the muscles of M.E. patients, their recording of muscle activity is grossly abnormal. The contraction is normal, but the relaxation of muscle fibres is slow and jerky, and at rest the muscle shows continuing activity (Howard, 1989). There might be an imbalance of magnesium and calcium across muscle cell membranes associated with this abnormality.

In spite of all the foregoing evidence of abnormalities in muscles of people with M.E., several studies have demonstrated 'that chronic fatigue syndrome is not a muscle disease. Muscle function is not impaired' (Wood, Edwards et al., 1991). However, the flaws in these studies have been (a) to ignore the muscle findings, and (b) to use patients complaining of chronic fatigue (e.g. in one study the patients were taken from those attending a 'fatigue clinic'), which includes patients who do not have M.E./PVFS. It seems most likely that the abnormal muscle fatigability found in typical M.E. has causes both in the muscle cells and also in the central nervous system.

Fibromyalgia

Fibromyalgia is a chronic condition characterized by muscle pain, tender points ('fibrositis'), stiffness and sleep disturbances. It has therefore some clinical features in common with M.E. and with CFS. In a study of primary fibromyalgia, only 7 out of 33 patients diagnosed as having primary fibromyalgia fulfilled criteria for CFS (Wysenbeek, 1991). It is probable that some people diagnosed as having fibromyalgia may have M.E. However, fibromyalgia responds to exercise therapy, to local injections into tender points and to low dose amitriptyline (a tricyclic antidepressant), which improves the sleep disorder. The sleep disturbance is a disorder of alpha EEG rhythm (part of a brain wave recorded during a sleep electro-encephalogram). Fibromyalgia symptoms may also be mediated by cytokines, as is true for CFS symptoms.