Chapter 4

What Causes M.E.?

II - Immunology, Red Cells and Neuropsychiatry

In those patients whose M.E. came on gradually, with no precipitating viral infection, it is possible that they had some previous virus which remained dormant in the body, not causing any immune reaction. Then for some reason there was *something which damaged their immune system,* thus lowering the body's resistance, and the latent virus became active and triggered the M.E. syndrome.

Factors which may injure the immune response:

- Viral infections - e.g. glandular fever, hepatitis
- Acute stress - emotional shock, accident or assault
- Prolonged unrelieved stress. There is a close relationship between emotions, the endocrine glands (hormones) and the immune system
- Immunizations [this connection remains unproven, however]
- Dietary deficiencies
- Environmental injury - such as from pesticides, ionizing or electromagnetic radiation, chemical pollution
- Bowel infestations - parasites (Amoeba, Guardia Lamblia), yeasts, bacteria. Intestinal parasites, particularly Guardia Lamblia, are suspected by some researchers to depress the immune system, and untreated intestinal Guardia could pave the way for developing M.E. later from an enterovirus. This may partly explain why there appears to be a high incidence of getting M.E. after a spell abroad. Diagnosis of Guardia Lamblia is difficult, and may involve a biopsy of the small intestine, or Guardia antibody in stool (Galland 1989, 1990).

The Immune System and M.E.

The picture of immunological abnormalities in M.E. is at present rather confused, because various studies have found a variety of abnormalities in different patient groups, sometimes with conflicting findings. So far there is no single test of immunological function that is consistently abnormal in 100 per cent of the cases. It can, however, be said that all the research results taken together do indicate that immune dysfunction occurs in M.E. syndrome.

These are some of the more significant studies:

Dr P.O. Behan (1985) and colleagues in Glasgow studied 50 patients with PVFS. The following immune abnormalities were found:

- Reduced function of lymphocytes to make protein
- Abnormal numbers and ratios of T-cells
- Circulating immune complexes were present in 25 per cent of the cases
- Auto-antibodies (antibodies to a patient's own tissue) to various tissues were found in many patients

Dr Lloyd (1989) of Australia investigated 100 M.E. patients.

Immune abnormalities were:

- Reduced levels of IgG1 (Immunoglobulin G1) and IgG3 in 56 per cent of the patients. (This finding was confirmed by a later study).
- Reduction in numbers of total lymphocytes and T-cells. T-cell function (cell-mediated immunity) was reduced in 88 per cent of the patients, compared to 1 per cent of the healthy population.
  '. . . this provides the strongest reported evidence of disordered T-cell function in patients with CFS:
- Increase of lymphocytes showing immune activation. 'Once activated these cells may continue to produce cytokines, which mediate the symptoms of CFS:
- Levels of Interleukin 1 (Klimas, 1991), also of Interleukin 2 (Cheney, 1989) have been measured in CFS patients and found to be much higher than normal.

Klimas et al. (1990): In this study of 30 CFS patients, the most consistent abnormality was *low natural killer (NK) cell cytotoxicity* - virally infected cells were not being killed properly. The authors state that their results: 'suggest that CFS is a form of acquired immunodeficiency. This deficiency of cellular immune function was present in all the subjects that we studied'

Komaroff and Buchwald (1991), in a review of all laboratory findings in CFS, comment on the inconsistency of immune abnormalities:

> In some studies, even those who meet the case definition of CFS may have been suffering from different illnesses in which fatigue is the common denominator. Tests are obtained at various points in the clinical course, a circumstance that makes it difficult to determine if abnormalities are transient or fluctuate over time.

That is, immunological findings may vary at different stages of the illness.

The authors summarised all the most consistent findings from all published immunology research:

- Depressed numbers and function of natural killer cells
- Low levels of circulating immune complexes
- Low levels of several auto-antibodies, particularly antinuclear and antithyroid antibodies
- Altered levels of immunoglobulins
- Abnormalities in the number and function of lymphocytes

The most recent findings of abnormal immune function in M.E. (Landay et al., *Lancet,* 1991) indicate that there is *immune activation,* the degree of which is directly related to the severity of disease. Specifically, the abnormalities were in subsets of T8 suppressor cells - further details are too complex to describe here.

Of the patients who were severely ill (capable of less than 25 per cent of normal daily activity), 85 per cent had one or more abnormal results; whereas of those patients who had largely recovered, only 10 per cent had abnormal results. The abnormal immunological markers were not found in healthy controls, nor in groups of patients with conditions such as depression, chronic fatigue alone, acute viral infections, and SLE (a chronic systemic illness).

Red Blood Cell and Cell Membrane Abnormalities

Dr Mukherjee (1987) and colleagues in Australia examined red blood cells from seven M.E. patients at the time of a clinical relapse. In four cases, some of the red cells showed an abnormal shape. Such abnormal red cells had previously only been seen in the blood of runners after a marathon. M.E. sufferers in relapse say 'I feel as though I have run a marathon' after minimal exertion. On retesting three weeks later, when the patients felt better, there were no abnormal red cells.

Dr Simpson (1989) of New Zealand looked at red blood cells from 102 patients with M.E., also from 52 healthy controls and 99 Multiple Sclerosis (MS) patients. Samples from M.E. cases had 'the highest incidence of cup forms and the lowest percentage of normal red cells'.

The significance of these research findings is the fact that red cells have to change shape slightly to pass through minute blood vessels (capillaries), which they can do if they have the normal bi-concave disc shape and a flexible outer coat. If some cells are deformed then these might not squeeze so easily through capillaries, resulting in reduced blood flow and oxygen supply to some tissues.

Dr Simpson (1991) found identical red cell abnormalities in blood from M.E. patients in California, Western Australia and the UK, associated with M.E. symptoms. Vitamin B_{12} injections led to improvement in well-being within 24 hours, and loss of symptoms was associated with reduced numbers of abnormal red cells in half the cases.

There are symptoms suggesting impaired blood flow in M.E.: areas of poor perfusion in the brain, poor muscle performance during exercise, impairment of cognition and other intellectual functions (as after a stroke), and poor circulation in the hands and feet.

A possible explanation of abnormal red cells in M.E. came from Dr Wakefield (1989): Excessive cytokine production, e.g. interferon, due to persistent viral infection, can produce structural changes in cell membranes, this could account for some deformed red cells in patients in relapse.

In a study on 25 CFS patients (Kajid, 1991), all of whom had red cell membrane abnormalities, LV. infusion of 15 gm ascorbic acid (vitamin C) led to significant return to normal of the red cells. Further studies are needed, yet this gives some rationale to the anecdotal reports from some patients of the benefit of high doses of infused vitamin C.

Magnesium in Cells

A study at Southampton (Cox et al., 1991) found low levels of magnesium in red blood cells of subjects with M.E., compared with healthy controls. A therapy trial of magnesium injections produced improved symptoms and stamina in 80 per cent of the M.E. patients, and raised their red cell magnesium levels to normal.

The reason why intracellular magnesium appears to be low in M.E. is not clear, and the above study is being repeated.

Neurological Abnormalities in M.E. and CFS

Possibly the most crippling disability, especially in the long-term patient, is the loss of intellectual abilities, collectively known as 'cognitive dysfunction'. This is what causes many M.E. people, who in their thirties and forties are skilled professionals, to lose their jobs. Physical disablement is hard enough but can be coped with; many other people with physical disability can function intellectually and hold jobs, compute, create, and contribute some wage-earning activity to society.

When someone of normal or above-average intelligence finds that his or her memory, concentration, comprehension, even speech is disturbed by this disease, is it any surprise that he or she becomes depressed and anxious? As well as cognitive dysfunction, emotional disturbance is common with M.E.: depressive symptoms, acute anxiety, panic attacks, and sometimes euphoria and mania. This kind of emotional lability is also common in MS.

Depression and anxiety are such common symptoms of M.E. that some doctors attribute all the M.E. symptoms to untreated depression.

However, depressive symptoms commonly occur with any chronic illness. A depressed person 'suffers from lowering of mood, reduction of energy, and decrease in activity. Capacity for enjoyment, interest and concentration are impaired, and marked tiredness after minimum effort is common' (International Classification of Disease). But this is not a description of someone with M.E., who typically is well motivated, enjoys things he or she is capable of, and does not have sustained lowering of mood. Depressive symptoms, especially profuse weeping, are directly associated with exhaustion, fever and feeling very ill (perhaps as a result of from cytokine activity?), and usually improve with rest.

> Diminished ability to think, concentrate or remember may be caused by an organic mental disorder, and are not useful symptoms for making a diagnosis of a major depressive episode in the medically ill. Since fatigue and loss of energy are so commonly caused by physical illness, these vegetative symptoms cannot be used to make a diagnosis of major depression.
>
> *(Cavanaugh, 1991)*

If you take a number of people with M.E. (not just 'chronic fatigue'), who have a condition causing a brain disturbance with disordered neurotransmitters, and excess cytokine production by activated white cells; an illness which makes many lose much of their lives jobs, family, friends and sports; an illness with debilitating exhaustion, pain, and malaise - would you not expect those affected to show emotional disturbance some of the time?

If you modified these emotional symptoms, would you expect to cure the underlying disease?

There is also a relatively high incidence of depression in other diseases that affect the brain, including Alzheimer's, MS, Parkinson's disease and Huntingdon's disease (Schiffer, 1990).

In one survey of people with MS, it was estimated that 'the lifetime risk of depression is 40-50 per cent, and that cognitive deficits are present in 60-70 per cent [of the] patients' (Stenager, 1990).

In another study of MS, it was found that an increase in emotional disturbance coincided with an increase in disease activity (Dalos, 1983). About 80 per cent or more of MS patients suffer from severe, disabling fatigue; another similarity with M.E.

In some M.E. research studies there is not a strict enough case definition for patients, and probably much less than half of cases with 'chronic fatigue' have M.E. or post-viral fatigue syndrome. In one study, only 5 per cent of patients presenting with 'chronic fatigue' fulfilled the American case definition for the Chronic Fatigue Syndrome (Manu, 1991).

Neurological Research Findings in M.E. and CFS

There is *now evidence that the cognitive dysfunction represents organic neuropathology* - there is something wrong in the brain that can be seen or measured.

The following findings were presented at two meetings - at Los Angeles, February 1990, and at the M.E. Symposium at Cambridge, April 1990:

Dr Carolyn Warner, who specializes in MS, found neurological symptoms in many CFS cases, the most prominent being balance disturbance. On certain neurological tests patients lose balance and fall over, and more complicated tests of vestibular function are abnormal.

Dr Shiela Bastein, (Berkeley, CA) carried out a range of *neuropsychometric testing* on 175 people with CFS. These tests pick up different defects in cognitive function. She found definite abnormalities which, when put together, made an identifiable pattern of dysfunction unique to CFS.

Magnetic Resonance Imaging

(MRI - same as nuclear magnetic resonance) brain scans are done regularly on other patients with neurological diseases, and have been performed on many CFS patients of all age groups in the USA. The abnormalities on MRI scans indicate patches of inflammation in various areas of the white matter of the brain.

In the Lake Tahoe epidemic, 80 per cent of patients had brain MRI lesions. In California, endemic (isolated) cases also were 80 per cent positive (compared with 21 per cent positive in healthy controls). Non-specific MRI changes in brain scans increase with age; this causes scepticism about MRI findings in CFS patients. However, Dr Cheney looked at positive MRI scans in different age groups; in ill teenagers with CFS over 50 per cent had abnormal MRI scans - quite abnormal for this age group.

Northern Nevada Epidemic Data

Daugherty and colleagues carried out cognitive function testing on 20 CFS patients and 20 healthy controls, and found significant dysfunction in 19 of the 20 CFS patients. The most marked and frequent defects were in attention-concentration, problem solving, kinesthetic ability, and verbal memory.

MRI scans were done on 15 of these patients and 16 controls. There were abnormalities in *all* the CFS patient scans, but only one from the healthy control group. 'The striking distortion along with the abnormal results of MRI scans in these patients suggest a pathological process in the brain. *The pattern of focal and lateral impairments is more consistent with that of an atypical organic brain syndrome, than of anxiety and depression'* (Daugherty, 1991).

A comprehensive survey was carried out in the USA (Buchwald et al, 1992) in which 259 patients were studied, all of whom had an illness that started abruptly after a 'flu-like' episode. They all had features of disabling chronic fatigue and impaired cognition. Results of the study included:

- MRI brain scans showed scattered sub-cortical foci of inflammation in 78 per cent of the patients.
- A higher average ratio of *CD4/CD8* T-cells than in healthy controls.
- Active replication of human herpes virus type 6 (HHV-6) in 70 per cent of patients.

The authors comment that 'neurological symptoms, MRI findings, and lymphocyte studies suggest that the patients may have had a chronic, immunologically mediated inflammatory process of the central nervous system. The active replication of HHV-6 most likely represents reactivation of latent infection, perhaps due to immunologic dysfunction:

SPECT Scan

This technique looks at blood perfusion of the brain. Professor Ismael Mena did a study of SPECT scans on CFS patients and on healthy controls. He found perfusion defects in 71 per cent of the CFS patients, mainly of the right temporal lobes. He did a further test in which CFS patients exercised on a bicycle. Their SPECT scans were repeated after vigorous exercise (when blood carbon dioxide had returned to normal), and there was a *decrease* in blood flow to the brain, mainly in the temporal and frontal lobes. The expected result would be an increase in cerebral perfusion after exercise (Mena, 1991, *CFIDS Chronicle).*

The SPECT scan abnormalities are especially interesting because they corresponded with the neuropsychometric data, which said that the temporal lobe was most likely to be affected - based on knowledge of various psychological functions of different areas of the brain cortex. This clinical and laboratory correlation makes a powerful argument for there being some abnormality of the brain in M.E./CFS.

Electro-Encephalo-Gram

Dr Jamal, of Glasgow (who did single-fibre EMGs) found EEG abnormalities in 85 per cent of 20 PVFS patients tested. These changes suggested a patchy disturbance of cerebral function.

Hypothalamic Function Studies

The control centre of many bodily functions - e.g. appetite, temperature, blood sugar, sleep pattern, sweating, mood, libido, body weight - is in the hypothalamus (part of the mid-brain). M.E. symptoms include upset of many of these functions, so research in the UK and USA has looked at hypothalamic function.

In Glasgow, studies have shown that patients with PVFS/M.E. have abnormal water balance - when a loading dose of water is taken, the hypothalamus does not regulate the hormone that tells the kidneys to conserve or flush it out, and patients tend to retain water. This might partly explain the erratic weight gain of such patients. Such water-retention also occurs in irritable bowel syndrome and premenstrual syndrome.

Further work, testing the hypothalamic response to a substance called *busiprone,* compared the response of PVFS patients to that of patients with primary depression. The PVFS patients showed a significant rise in the amount of the hormone *prolactin,* but the depressed group had no rise in prolactin. This prolactin response is a way of testing *5-hydroxytriptamine* (5HT, a chemical that affects mood) receptors in the hypothalamus (Behan, 1991, *British Medical Bulletin).*

Other recent research on the hypothalamus has shown evidence of a fault in the hypothalamus-pituitary-adrenal hormone regulating system. This fault appears to be a deficiency in *Corticotrophin Releasing Hormone* (CRH) from the hypothalamus. The end result in the patient is abnormally low levels of plasma cortisone in the evening, and reduced 24-hour urine excretion cortisol levels. This is a simplification of the published research paper, which is very complex (Demitrack et al., 1991).

However, the authors point out that 'glucocorticoid [a cortisone hormone] deficiency can result in immune abnormalities perhaps sufficient to contribute to the exacerbation of allergic responses and raised antibody titres to a variety of viruses that are seen in CFS patients.' Viral infections may affect hypothalamic CRH release by altering neurotransmitters. This recently published research may prove to have further implications for unravelling the complex symptoms of M.E.

Some young M.E. patients have been seen with Parkinsonism, which usually gets better in a year. Iceland researchers have also found a higher-than-expected incidence of Parkinson's disease among the now middle-aged people who were involved in the 1948 Iceland M.E. outbreak.

Most M.E. symptoms, including Parkinsonism, memory loss and the hypothalamic dysfunctions, could be explained by upset of the mid-brain functions - one could call it a 'mid-brain syndrome'.

Other Studies of Behaviour and Cognitive Functions

Hickie and others in Australia (1990) assessed 48 patients who fulfilled criteria for CFS, using a range of psychological interviews and tests, and compared data with that from 48 matched controls who had depression.

Of the CFS group, 80 per cent reported the following psychological symptoms:

Poor concentration - 52 per cent
Poor short-term memory - 27 per cent
Depression - 38 per cent

The pre-illness rate of major depression and all psychiatric disorders was no higher than that within the general community. In addition, the pattern of psychological symptoms was found to be significantly different to that of the depressed control group, and severe depression was rare.

The researchers concluded:

> There is no evidence from our well-defined sample to support the hypothesis that CFS is a physical variant or expression of a depressive disorder. Instead, our study supports the hypothesis that the current psychological symptoms of CFS are a consequence of the disorder, rather than evidence of antecedent vulnerability.

In the UK, Prasher, Findlay and colleagues (1990) measured sensory-evoked and auditory event-related cognitive potentials in 37 patients diagnosed with M.E., and in 25 healthy controls. A *potential* here means measurement of an electrical change in the brain that results from a stimulus - a sound stimulus, or a peripheral nerve stimulus, or a visual one.

There were no abnormalities found in the pathways of sensation of vision, sound or from peripheral nerves. However, cognitive potentials that measured attention and efficiency of information processing (identifying two different sounds, and responding to them) were different in the patients. 'The abnormalities indicate attentional deficits in some patients and speed of information processing in others. The prolonged latencies observed in these patients have not been observed in patients with depression in many other studies:

Andrew Smith (psychologist, University of Cardiff ongoing research) uses tests of performance efficiency in patients with evidence of chronic viral infection (VP1 positive or abnormal muscle biopsy) and controls. The test results so far show that M.E. patients have:

- Impaired motor function
- Greater sensitivity to visual stimuli
- Slower ability to search for targets
- Increased distractibility
- Impaired short-term memory

These results suggest that behavioural measurements may help to distinguish between chronic enteroviral illness and depressive illness.

So, after all these studies looking at the illness from many different aspects, what is causing the M.E. syndrome?

a) There is a persistent virus infection in some cases.
b) Something has upset the immune response: A previous virus? A new virus? Environmental factors? Stress? Parasites?
c) Physical overexertion at the time of an infection may have an adverse effect (as with polio).
d) Probably some inherited predisposition
e) Continuing immune response produces excess circulating cytokines, which may be damaging cell membranes, impairing blood flow, and interfering with brain function.
f) Continuing psychological factors may be perpetuating the illness in some cases.

If you are confused after reading about some of the research into M.E., you are not alone! There is as yet no single expert who can explain exactly what causes M.E. and the mechanisms of all its distressing symptoms.

There may be some alarm and confusion arising from the publicity about HIV/AIDS and its causes, and a possible link with M.E. In M.E. there may be some abnormal immune response, *but this* is *quite different to the immune collapse seen in HIV/AIDS.*

Work at Middlesex Hospital, London, using SPECT scans has found abnormalities in brain perfusion in patients with postviral fatigue syndrome (Costa, et al., BMJ 1992, vol 304, p. 1567). Scans from 14 patients with M.E. showed 'a significant reduction of perfusion to several areas of the brain, particularly the brain stem'. These abnormalities were not found in controls.