ME/CFS/PVFS

An exploration of the key clinical issues

Prepared for health professionals and members of The ME Association by

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CONTENTS

1. Introduction

Most doctors now accept that ME/CFS/PVFS is a genuine and disabling illness. The World Health Organisation classifies ME as a disease of the central nervous system (reference: International Classification of Diseases 10, G93.3) and the Department of Health officially recognises it to be a 'debilitating and distressing condition' (reference: House of Commons debate, 13/11/91, Hansard col 582W). However, disagreements and uncertainties remain – especially over nomenclature, causation and the most appropriate forms of management.

2. Nomenclature

A disease of many names

- ME (myalgic encephalomyelitis) is a name which was originally introduced in a *Lancet* editorial (Leading Article, 1956) to describe people with the illness who had been admitted to London's Royal Free Hospital during 1955. Clinically, myalgic was used to refer to the characteristic muscle symptoms; encephalomyelitis to the brain symptoms. Pathologically, encephalomyelitis indicates inflammation within the brain and spinal cord – pathology for which there is now very limited evidence (Schwartz *et al* 1994).
- CFS (chronic fatigue syndrome) is the name currently favoured by the medical profession because it makes no firm assumption about cause. Two major criticisms of CFS as a name are that it fails to reflect the severity of the illness and it has become a convenient label for anyone with unexplained fatigue. It should also be noted that CFS as currently defined in section 3 is designed to select homogeneous groups of patients for research purposes and is not intended for the routine clinical assessment of what is a very heterogeneous group of patients.
- PVFS (post-viral fatigue syndrome) was introduced during the 1980s as a description for patients who could clearly trace the onset of their illness back to a viral infection.

The current situation

The term encephalomyelitis is no longer an appropriate or accurate pathological explanation for what may be happening within the nervous system in this illness. It now appears that alterations in brain chemicals and hormones, with autonomic dysfunction, provide a more rational explanation for many of the key symptoms.

Having accepted the inaccuracy of the term encephalomyelitis, The ME Association plans to substitute the word encephalomyelitis with encephalopathy, meaning an abnormality of brain function. We believe that encephalopathy is now the most appropriate description for the various central nervous system abnormalities (*ie* hypothalamic, autonomic and cognitive dysfunction; cerebral hypoperfusion) that have been reported in the research literature (see section 5:4).

The debate about nomenclature is ongoing and The ME Association will also continue to use the term ME/CFS in its literature in accordance with its restated charitable object that is 'to offer relief to persons of all ages with ME/CFS through the provision of information and to further education in all aspects of the illness and to support research and to publish the useful results of such research'. In America, the Department of Health and Human Services has established a Name Change Workgroup with the remit of exploring options surrounding a possible change in name.

3. Research based definitions

A number of consensus-driven, criterion-based definitions for CFS have now been agreed upon and published. The definition produced by the US Centers for Disease Control (Fukada *et al* 1994) is used widely for research purposes but it has a number of defects (*eg* the requirement for symptoms to be present for six months before a diagnosis can be made) that limit its use in clinical practice.

Table 1

CDC Criteria

1) Clinically evaluated, unexplained, persistent or relapsing chronic fatigue that is of new or definite onset (has not been lifelong); is not the result of ongoing exertion; is not substantially relieved by rest; and results in substantial reduction in previous levels of occupational, educational, social, or personal activities; and

2) the concurrent occurrence of four or more of the following symptoms, all of which must have persisted or recurred during six or more months of illness and must not have predated the fatigue:

   - Self-reported impairment in short-term memory or concentration severe enough to cause a substantial reduction in previous levels of occupational, educational, social or personal activities
   - Sore throat
   - Tender cervical or axillary lymph nodes
   - Muscle pain
   - Headaches of a new type, pattern or severity
   - Unrefreshing sleep
   - Post-exertional malaise lasting more than twenty-four hours
   - Multi joint pain without joint swelling or redness

4. Epidemiology

Who contracts ME/CFS?

A small number of epidemiological studies, mainly based on the CDC diagnostic criteria, have been carried out in America, Australia and the UK. One recently published community-based survey (Jason *et al* 1999) – which involved a sample of 28,673 adults – found that 4.2 per thousand had CDC defined CFS.

Results from other published epidemiological studies indicate:

- A prevalence figure of at least two per thousand of the adult population (*ie* around 150,000 people in the UK or between three and six cases on the average general practitioner list).
- That all age groups are affected although onset is rare below the age of seven and above the age of 60.
- The most common age of onset is between mid-teens and mid- forties.
- A slight female:male predominance, which is as yet unexplained.
- ME/CFS affects all social classes and ethnic groups.

5. Pathoaetiology

Relevant research findings

ME/CFS is an heterogeneous disorder, not only from the point of view of clinical presentation, but also from the contribution made by various different factors which may be involved in the perpetuation of symptoms.

5:1 Role of infection

Although ME/CFS is precipitated frequently by a viral infection, there is no really convincing evidence to indicate that persistent systemic infection – viral or bacterial – is responsible for the perpetuation of symptoms. However, it should be noted that ME/CFS symptoms are very similar to those of post-polio syndrome (Bruno *et al* 1995) and that viral injury to excitable tissues such as muscle and nerve has the potential to alter their critical metabolic functions. These include ion channel transport, mitochondrial function, and the response to circulating neurotransmitters and neurohormones – alterations which are capable of persisting well after apparent recovery from a precipitating infection (Oldstone 1989).

Disruption in immune responses in ME/CFS may also allow the reactivation of common latent viruses such as Epstein-Barr and HHV6, as well as preventing the effective clearance of endemic viruses (*eg* enteroviruses).

It has recently been suggested that there may be dysregulation of the interferon-induced 2-5A synthetase and protein kinase R antiviral pathways in ME/CFS (Suhadolnik *et al* 1997). These preliminary findings need to be replicated in better studies which include more appropriate controls (*ie* those with a recent viral infection), before any firm conclusions can be drawn.

5:2 Immunology

Two basic problems with immune function have been reported. First is evidence of immune activation as demonstrated by modest elevation of numbers of activated T lymphocytes, particularly cytotoxic T cells, as well as elevations in circulating cytokines in some studies. Second is poor cellular function with low natural killer cell cytology (NKCC), poor lymphocytic response to mitogens in culture and immunoglobulin deficiencies, often involving IgG1 and IgG3. Some studies have also found an increased incidence of autoantibodies in ME/CFS patients.

These findings tend to have a waxing and waning pattern that is consistent with episodic immune dysfunction. A frequently proposed hypothesis is that the immune dysfunction is triggered by an infection, or some other form of antigenic challenge. The immune dysfunction then persists as a result of neuroendocrine abnormalities (*ie* hypocortisolaemia), physiological dysfunction, and/or activation of latent viral infection (*ie* Epstein-Barr virus).

None of the abnormalities so far reported are sufficiently marked or consistent to make them useful for either routine clinical assessment or diagnostic purposes.

For a recent review of immunological dysfunction in ME/CFS see Patarca-Montero *et al* 2000.

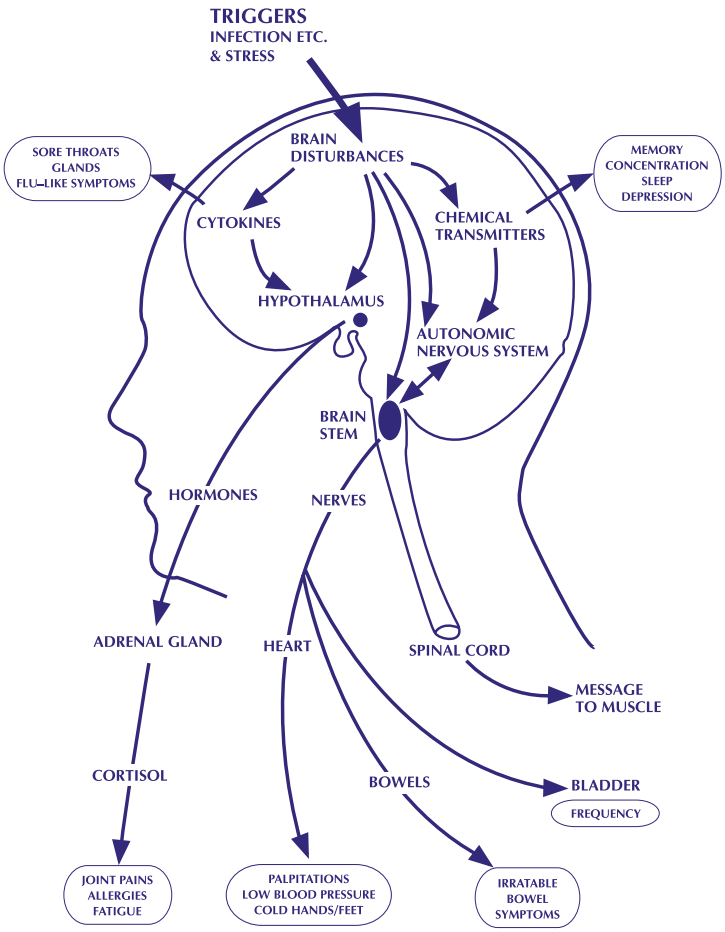
5:3 Muscle studies

A variety of muscle abnormalities have been reported, some of which are not consistent with the theory that muscle symptoms in ME/CFS are simply due to inactivity (Lane 2000). Objective evidence of post-exercise fatigue has recently been demonstrated using repetitive isometric quadriceps exercise testing (Paul *et al* 1999). Oxidative defects in muscle energy metabolism – as demonstrated by magnetic resonance spectroscopy – may be due to impaired blood flow to the exercising muscles, as a result of dysregulated autonomic control (McCully and Natelson 1999).

5:4 Central nervous system involvement

Accumulated research evidence suggests that central mechanisms are far more important in the production of mental and physical fatigue in ME/CFS than peripheral (muscular) abnormalities. These central mechanisms may in fact involve the basal ganglia (Chaudhuri and Behan 2000) – areas of the brain which are extremely sensitive to pro-inflammatory cytokines and direct viral invasion. Basal ganglia are also considered to be the key neural integrator for motor and motivational aspects of higher cortical and limbic activities.

How ME/CFS may be affecting the brain and central nervous system



Source: *Living with ME,*
Charles Shepherd, Vermilion, 1999

■ Autonomic dysfunction and neurally-mediated hypotension

Several studies have demonstrated that disturbances in the autonomic regulation of cardiovascular reflexes can be found in a subgroup of ME/CFS patients (Bou-Holaigah *et al* 1995). Neurally-mediated hypotension (NMH) can be induced by tilt-table testing, which involves a patient lying on a table and then tilting the table upright to 70 degrees for 45 minutes whilst the heart rate and blood pressure are continually monitored. Patients with NMH develop low blood pressure under these conditions as well as presyncopal symptoms such as nausea, sweating and light-headedness. Although the use of fludrocortisone has been recommended as a form of treatment for ME/CFS patients with proven NMH, the results of two

clinical trials (Peterson *et al* 1988; Rowe *et al* 2001) have failed to demonstrate any benefits.

■ Hypothalamic dysfunction

Key symptoms such as fatigue, sleep disorder and disturbed thermoregulation are all consistent with hypothalamic dysfunction. Disturbances in hypothalamic function in ME/CFS are supported by several studies which have examined the hypothalamic-pituitary-axis control of cortisol production and the way in which arginine-vasopressin controls water metabolism (Bakheit *et al* 1993). The most consistent finding relates to disturbances in the hypothalamic-pituitary-adrenal axis, *ie* hypocortisolaemia (Demitrack *et al* 1991) and adrenal gland atrophy (Scott *et al* 1999), which may be the result of lowering of central corticotropin-releasing hormone levels (Altemus *et al* 2001).

■ Neurotransmitters

Evidence of abnormalities in neurotransmitter function, particularly involving serotonin, acetylcholine and dopamine, comes from a number of published studies.

Growth hormone (GH) secretion from the anterior pituitary is augmented by acetylcholine, and pyridostigmine has been used as a probe to stimulate acetylcholine-mediated growth hormone release. When given pyridostigmine, ME/CFS patients (as well as those with a similar syndrome following organophosphate pesticide exposure) show an exaggerated response (Chaudhuri *et al* 1997). Acetylcholine supersensitivity has also been observed in a study which assessed the skin microcirculation in ME/CFS patients (Spence *et al* 2000) – a finding which may be related to symptoms that involve vascular integrity.

Prolactin release from the anterior pituitary is under the inhibitory control of dopamine, and is stimulated by serotonin. Buspirone, an indirect serotonin agonist, produces an exaggerated serotonin-mediated release of prolactin in ME/CFS patients when compared to healthy controls and those with depression (Bakheit *et al* 1992).

■ Neuroimaging

Evidence of regional cerebral hypoperfusion using SPECT (single-photon emission tomography) scans has been reported in a number of studies. Of particular interest is a finding of brain stem hypoperfusion (Costa *et al* 1995) which has not been found in patients with any other medical or psychiatric condition. MRI (magnetic resonance imaging) scans have demonstrated white matter abnormalities that may be consistent with a previous infection involving the central nervous system (Lange *et al* 1999).

Further evidence of subtle neuropathology comes from a more recent study which has demonstrated enlargement of cerebral ventricular volumes (Lange *et al* 2001).

■ Psychological testing

More than twenty different studies on various aspects of cognitive dysfunction in ME/CFS have now been published. They confirm that the frequently reported clinical observations of problems with memory, concentration and attention span (particularly the ability to process incoming information) are genuine and cannot simply be explained by the presence of co-existent psychiatric disorders such as depression (DeLuca *et al* 1997). For a recent review of neuropsychological functioning in ME/CFS see Michiels and Cluydts 2001. (See also section 5:6 on p5).

5:5 Ion channels, resting energy expenditure and Syndrome X

It has recently been proposed that dysfunctional ion channels may be a key abnormality in the cellular pathogenesis of ME/CFS (Chaudhuri *et al* 2000). This is related to the fact that an ME/CFS-like syndrome develops after ciguatera fish poisoning (Pearn 1997) and ciguatoxin is a potent inhibitor of neuronal sodium channel activity. Changes in neuronal ion channel function could account for the altered neuroendocrine functions so far reported in ME/CFS as well as helping to explain the fluctuation in fatigue and other symptoms which are a key feature of the illness.

Resting energy expenditure (REE) is the energy expended by an awake, alert subject in the post-absorptive state. It accounts for between 60% and 90% of total energy expenditure. A significant rise in REE is found in ME/CFS patients when compared to controls (Watson *et al* 1998), and as 30% of REE is expended to maintain physiological ion gradients in normal health, a cell membrane defect causing ion leakage will increase the REE. Higher levels of REE are also found in patients with sarcoidosis who have profound fatigue.

Ion channel dysfunction may also help to explain the basis of Syndrome X – an unusual cardiac condition which appears to be associated with ME/CFS (See also section 6:4 p6).

5:6 Psychiatric co-morbidity

Research in this area has tended to concentrate on the incidence of co-existent psychiatric disorders, the possible role of abnormal illness behaviour and the value of CBT (cognitive behaviour therapy) as a form of treatment. Whilst some studies have reported relatively high rates of co-morbid depression (Wessely and Powell 1989), others have found levels which are very similar to those in other chronic medical conditions (Shanks and Ho-Yen 1995). The way in which abnormal illness behaviour and illness attributions (particularly about cause) may be perpetuating ill-health and disability in some ME/CFS patients remains a contentious issue (Deale *et al* 1998).

The overlap of ME/CFS symptoms and psychiatric disorders such as depression can result in patients being misdiagnosed and given inappropriate psychiatric labels. In fact, one study carried out by psychiatrists (Deale and Wessely 2000) found that 68% of a sample of 68 patients attending their ME/CFS clinic had been misdiagnosed as having a psychiatric illness, and in most cases there was no evidence of any previous or current psychiatric disorder (see section 6:7 p7).

5:7 Sleep disturbance

ME/CFS patients complain commonly of hypersomnia in the initial stages of their illness. This is then followed by a general decrease in sleep efficiency once the illness enters a more chronic stage. Reported sleep disturbances include difficulty in initiating sleep, frequent wakening during the night and vivid dreams. Periodic jerking limb movements and 'restless legs' are also quite frequently reported.

A variety of anomalies in normal sleep pattern have been reported, including changes in alpha non-rapid eye movement (Moldofsky 1989), which may be acting as perpetuating factors. One recent study concluded that there was very little evidence to support the hypothesis that ME/CFS patients with a concurrent diagnosis of anxiety, depression or somatisation disorder have any more sleep disorders than those with no psychiatric disorder (Morris *et al* 1997). So it appears that sleep disorder in ME/CFS may be an integral part of the disease process.

Whatever the cause, sleep disturbance is one symptom which the physician should always aim to identify and manage (see also section 7:2 p9).

6. Diagnostic assessment

6:1 When to consider making a diagnosis of ME/CFS

A period of debility frequently follows many acute infections. However, when this persists beyond a few weeks in a previously healthy individual, consideration should be given to making a diagnosis of a post-infectious fatigue state as there is a considerable amount of anecdotal evidence to suggest that appropriate management (*ie* rest, followed by convalescence and a gradual return to normal activities) at this stage can play a role in reducing long-term morbidity.

Where symptoms persist beyond two or three months, and the person concerned has been unable to resume his normal way of life, then serious consideration should be given towards making a diagnosis of ME/CFS. This should include baseline investigations, as well as other investigations if particular symptoms (*ie* neurological, rheumatological, gastrointestinal) are more prominent than would normally be expected in someone with ME/CFS (see also section 6:6 p7). The differential diagnosis of ME/CFS is considered in more detail in Table 2 p8.

Patients who present with ME/CFS-like symptoms should be treated with compassion and carefully evaluated. They seldom look as ill as they feel, and so friends, family, employers and even doctors may have doubts about whether they are genuinely ill.

6:2 Onset: how does ME/CFS usually start?

- Some form of viral infection (*eg* flu-like illness, glandular fever, tonsillitis, meningitis, encephalitis, hepatitis) is the most common precipitating factor.
- Less common triggers include vaccinations (*eg* hepatitis B), toxins (*eg* ciguatera poisoning), pesticide exposure (organophosphates) and major stressful events.
- In a minority there is no clear precipitating factor and the onset may be more insidious.

6:3 Taking a clinical history

With a diagnosis of ME/CFS being made largely on a patient's clinical history, questions should address:

- Previous medical and psychiatric illness.
- Previous operations and blood transfusions (? possibility of hepatitis C infection).
- Occupational history including exposure to chemicals, solvents and pesticides.
- Possible precipitating events (*eg* infections, vaccinations, toxins, severe stress, trauma or surgery, athletic overtraining).
- Clinical features (*eg* weight loss, prominent arthralgia, transient neurological events) which indicate that other possible diagnostic explanations need to be pursued.
- Social history (? possibility of HIV infection)
- Family history (? other members with an ME/CFS-like illness).

Establishing a clear picture of the effects of ME/CFS on a patient's lifestyle is important when it comes to management and benefit entitlement. Questions should therefore be asked about employment, education, family responsibilities and the degree of functional impairment that is occurring.

6:4 Symptoms

Predominant symptoms in one patient may be quite different to those seen in other ME/CFS patients. Some are affected predominantly by mobility problems whereas others find problems with cognitive functioning or pain to be far more disabling.

However, the core symptom of ME/CFS is fatigue, which usually affects both physical and mental functioning. One of the most striking features of this fatigue is the way in which patients describe how even minor amounts of physical exertion can produce a marked exacerbation in muscle fatigue/pain *etc*, often accompanied by several other symptoms. It may then take days or even weeks after such a relapse before they return to a more 'normal' level of activity.

Key symptoms for making a diagnosis of ME/CFS are:

- Exercise-induced muscle fatigue.
- Post-exertional malaise: a delayed onset of symptoms following exertion.
- Myalgia (present in varying degrees in up to 75% of patients) and fasciculations, including blepharospasm.
- Cognitive dysfunction: problems with short-term memory, concentration and attention span (especially affecting visuospatial tasks) and anomia (difficulty in naming common objects) or dysnomia (the inability to give objects a correct name). Cognitive dysfunction alone is often severe enough to cause a substantial reduction in previous levels of occupational, educational, personal and social activities.
- A general feeling of on-going flu-like malaise.

Other symptoms which are **consistent with a diagnosis** of ME/CFS include:

- Dysequilibrium and orthostatic intolerance: feelings of unsteadiness are more frequently reported than vertigo.
- Autonomic dysfunction: particularly affecting circulation (postural hypotension and orthostatic tachycardia) and thermoregulation (night sweats, hypersensitivity to temperature extremes).
- Sleep disturbance: non-refreshing pattern which can include both hypersomnia (early in the illness), reversal of sleep rhythm (especially in children) and insomnia.
- Sensory disturbances: paraesthesiae and sometimes hemisensory pain or dysaesthesia.
- Hyperacusis and/or photophobia.
- Arthralgia but not including swelling, redness or joint deformity.
- Digestive symptoms: nausea and motility disturbances.
- Alcohol intolerance.
- Recurrent sore throats and tender cervical or axillary lymph nodes.
- Headaches of new type, pattern or severity.

The symptoms follow a characteristic pattern of both variability (often throughout the course of a day) and chronicity. Patients will often describe how they experience 'good days' and 'bad days' with fluctuations in severity being influenced by physical activity, stress, infections and temperature excesses.

There also appears to be an increased incidence of Syndrome X (anginal-type chest pain with normal coronary arteriogram but abnormal thallium 201 SPECT scan results) and a tendency to develop allergic conditions (Straus *et al* 1988) as the illness becomes chronic.

6:5 Physical examination

Although this is usually unremarkable, a full physical examination is mandatory to exclude other possible diagnoses.

Tests of balance and vestibular function (*eg* Romberg and Fukuda) should be carried out in patients who complain of dysequilibrium. This may be due to vestibular dysfunction (Ash-Bernal *et al* 1995).

6:6 Investigations

The diagnosis of ME/CFS should essentially be made on the typical pattern of symptoms, with the exclusion of other possible conditions that can present with fatigue and general ill health.

Anyone who is suspected of having ME/CFS should have the following routine investigations:

- ESR or acute phase protein changes (*eg* CRP).
- Haemoglobin.
- White cell count and differential. NB: Minor abnormalities may be present, especially during the early stages of the illness.
- Routine biochemistry screen (urea, electrolytes, calcium *etc*)
- Liver and thyroid function. NB: There is an increased incidence of Gilbert's disease in ME/CFS (Cleary and White 1993).
- Creatine kinase (CK).
- Antibodies to gliadin or endomysium to screen for coeliac disease (Skowera *et al*, 2001). NB: check serum IgA concentrations as well.
- Urinalyses for protein, blood, sugar.

Significant abnormalities in any of the above routine investigations indicate that other diagnostic explanations need to be pursued.

Further selected tests may also be appropriate in some circumstances:

- Autonomic function tests (*eg* tilt-table testing) if autonomic symptoms, syncope or postural hypotension are prominent.
- Infectious disease screening if there is a possibility of chlamydia (Chia and Chia 1999), Epstein-Barr, HIV, hepatitis B/C, Lyme disease, mycoplasma, Q Fever *etc*..
- MRI brain scan if multiple sclerosis is considered possible.
- Muscle biopsy if CK raised.
- Rheumatology screen and autoantibodies if arthralgia is prominent. Also consider screening for infections which can cause arthralgia and fatigue (*ie* borrelia, brucella, campylobacter, cytomegalovirus, parvovirus, shigella and yersinia).
- Serum oestradiol and FSH if there is a significant premenstrual exacerbation of symptoms (Studd and Panay, 1996).
- Short synacthen (ACTH) test if plasma or urinary cortisol is low and symptoms are suggestive of Addison's disease (hypotension, low serum sodium and raised potassium)

Tests which cannot be recommended in normal circumstances:

- Assessment of antiviral pathways* such as RNase L (Suhadolnik *et al* 1997).
- EMG studies.
- Functional neuroimaging (*eg* PET or SPECT scans) – the only indications are for research purposes.
- Neuroendocrine challenge tests (*eg* buspirone-induced prolactin test)
- Urinary markers* (*eg* CFSUM)
- Screening for coxsackie antibodies (Miller *et al* 1991) or evidence of reactivation of HHV-6 infection.

Some of these investigations will reveal abnormalities (eg hypocortisolaemia, exaggerated prolactin response to buspirone challenge) which are consistent with the diagnosis of ME/CFS. However, their value in routine clinical assessment is very limited as results are unlikely to influence practical management decisions.

(* The presence of specific urinary markers and abnormalities in antiviral pathways is being assessed in research studies financed by The ME Association 2000/2001).

6:7 Mental health assessment

About a quarter of all patients with ME/CFS will experience true clinical depression (as opposed to just feeling 'fed up') during the course of their illness. The explanation probably involves a combination of endogenous (*ie* disturbances in neurotransmitters) and reactive (*ie* psychological distress associated with problems connected to work, education, doctors, benefits, family commitments *etc*) factors. A comprehensive mental health assessment, possibly involving

questionnaires, should be carried out for patients who have co-existent psychiatric/psychological symptoms.

It should, however, be noted, that results from mental health questionnaires need to be viewed with caution (Farmer *et al* 1996) and that formal tests of neuropsychological function seldom reflect the degree of impairment reported by these patients. And as already pointed out in section 5:6, a significant number of people with ME/CFS are being given inappropriate psychiatric diagnoses by their doctors.

Table 2

Differential diagnosis

Although extensive and elaborate investigations are seldom required, other causes of chronic fatigue must be considered where the history is atypical. Also remember that 'new' symptoms should not be ascribed automatically to ME/CFS.

CARDIOVASCULAR
Valve disease and claudication

ENDOCRINE AND METABOLIC
Addison's disease
Fluid Retention Syndrome
Hypothyroidism
Pituitary tumour
Thyrotoxicosis
Haemochromatosis
Hypercalcaemia
Hyponatraemia

GASTROINTESTINAL
Coeliac disease
Crohn's disease
Food allergy
Irritable bowel syndrome

HAEMATOLOGICAL
Anaemia

INFECTIONS
Brucellosis
Giardia
Hepatitis B or C
HIV
Leptospirosis hardjo
Lyme disease
Parvovirus
Post-polio syndrome
Toxocara (children)
Toxoplasmosis

MALIGNANCY
Hodgkin's lymphoma

NEUROMUSCULAR
Multiple sclerosis
Myasthenia gravis
Parkinson's disease
Rare myopathies

PSYCHIATRIC
Anxiety +/- hyperventilation
Depression
Post Traumatic Stress Disorder
Somatisation

RESPIRATORY
Sarcoidosis
Tuberculosis

RHEUMATOLOGICAL
Fibromyalgia
Sjogren's syndrome
Systemic lupus erythematosus

MISCELLANEOUS
Alcohol or drug abuse
Allergies
Organophosphate pesticides
Sick building syndrome
Sleep apnoea
Narcolepsy
Various prescribed drugs

7. Management

7:1 Who should manage patients with ME/CFS?

Provided the diagnosis is not in doubt, the management of early straightforward cases of ME/CFS should be carried out by general practitioners and other members of the primary healthcare team. During the early stages (*ie* the first six months) this will involve giving appropriate advice about lifestyle modification, providing symptomatic relief through the careful use of drugs, and dealing with problems which may arise relating to employment, benefits and social support.

If the illness becomes more chronic and/or severe, consideration should be given towards referring the patient to a hospital specialist who is genuinely interested and informed about ME/CFS. In some parts of the UK (*eg* Dorset and Norfolk), multidisciplinary ME/CFS clinics are being established which permit easy access to occupational therapists, psychologists and other health professionals who may be able to play a useful role in the management of more difficult cases. Unfortunately, there are still many parts of the UK where general practitioners are unable to locate a single hospital consultant with the necessary expertise.

There are also a small number of tertiary referral centres where in-patient facilities and research into ME/CFS is being carried out. One such unit is the National ME Centre, Harold Wood Hospital, Romford, Essex RM3 9AR. NHS referrals for either out-patient or in-patient assessment are accepted from throughout the UK. For further information telephone 01708 378050.

7:2 Pharmacological treatments

A variety of drug treatments have been advocated for people with ME/CFS, but few have been subjected to well organised, randomised controlled trials (RCTs). At present, there is no single drug treatment that has been found to be generally effective in the majority of patients. However, there are a number of drugs which have been shown to be helpful in relieving symptoms such as myalgia and sleep disturbance.

People with ME/CFS are often more sensitive to the side-effects of drugs, particularly antidepressants, anaesthetics and those which act on dopaminergic transmission (eg metoclopramide/Maxalon). Consequently, it is often desirable to commence at a low dose, followed by gradual increases over a period of weeks when it comes to the use of antidepressant medication in particular.

Allergy Treatments

These should be directed at specific allergies that have been identified by reliable forms of allergy testing. There is no evidence from clinical trials to show that anti-allergy drugs such as terfenadine (Steinberg *et al* 1996) are of any benefit – unless a specific allergy has been confirmed.

Analgesics

When conventional first line analgesics (*eg* aspirin, paracetamol, NSAIDs) prove ineffective, it may be appropriate to prescribe a low daily dose (*ie* 10mg or 25mg) of amitriptyline. Anticonvulsants such as gabapentin/Neurontin and carbamazepine/Tegretol may be helpful in cases of more severe nerve pain that fail to respond to ordinary analgesics (Anon. *Drug and Therapeutics Bulletin,* 2000). Difficult cases should be referred to a hospital pain clinic for advice.

Antibiotics

There are anecdotal reports of patients improving following the use of antibiotics. Possible explanations include the way in which some antibiotics have immunomodulatory effects and the fact that some of these individuals may have had a persisting infection (*eg* Lyme disease or chlamydia) which responded to antibiotic therapy. Even so, there is no justification at present for the speculative use of prolonged courses of one or more antibiotics.

Antidepressants

A low dose of a sedating tricyclic antidepressant (*eg* 10mg or 25mg of amitriptyline taken before bedtime) may be helpful in the relief of myalgia or insomnia. Anyone who has co-existent clinical depression should be treated with a full course of an appropriate antidepressant or [possibly] St John's Wort.

Research studies indicate that there may be disturbances in the brain chemical transmitter serotonin in ME/CFS. However, the only large RCT (Vercoulen *et al* 1996) to assess the use of an SSRI (fluoxetine/Prozac) found no significant benefit.

Moclobemide/Manerix, a monoamine oxidase inhibitor, has been reported in an RCT to produce some benefits in key symptoms (Hickie *et al* 2000). The greatest reduction was found in patients with concurrent immunological dysfunction.

Antifungal Drugs

There is no scientific evidence to support the widely held view that candida/thrush, a common fungal infection, is in any way involved in ME/CFS (Dismukes *et al* 199l). Antifungal drugs such as nystatin should not therefore be prescribed.

Antihypotensives

The finding that some people with ME/CFS have low blood pressure/neurally mediated hypotension has led to the use of drugs such as fludrocortisone, which act by raising the blood pressure. The only RCTs (Peterson *et al* 1998 and Rowe *et al* 2001) to assess the value of fludrocortisone found no clear benefits.

Antiviral Drugs

Although viral infections commonly trigger ME/CFS, there is conflicting scientific evidence about the role of persisting viral infection being present. The only antiviral drug to be assessed in a clinical trial is acyclovir (Straus *et al* 1988). No benefits were found, so this form of intervention cannot be recommended.

Anxiolytics

Benzodiazepines are best avoided because of the real risks of dependency and problems when withdrawal is attempted.

Hydrocortisone and other hormonal treatments

Research studies have confirmed a number of hormonal abnormalities in ME/CFS (*eg* low levels of cortisol and DHEA) which may be contributing to symptoms and consequently are amenable to treatment.

- Clinical trials involving low doses of hydrocortisone have produced conflicting results. An American RCT (McKenzie *et al* 1998) found no obvious benefit whereas a more recent UK RCT (Cleare *et al* 1999), which used a slightly lower dose of hydrocortisone, did produce benefits with no evidence of suppression of the adrenal gland's natural output of cortisol.
- Deficiency of DHEA in ME/CFS has also been reported but no proper clinical trials have been carried out into the use of this controversial hormone.
- Oestrogen supplementation may be of value (Studd and Panay 1996) in women who have a premenstrual exacerbation of symptoms with low levels of serum oestradiol and FSH.
- There is no evidence of disturbed thyroid gland function in ME/CFS, and the use of thyroxine supplementation in people who have normal thyroid function tests is a controversial form of treatment which carries a number of risks, including the potential complication of precipitating an Addisonian crisis in patients with hypocortisolaemia (Shepherd 1997).

Hypnotics

Sleep disturbance in ME/CFS is a symptom which should always be taken seriously because even fit healthy people cannot function effectively without five hours solid uninterrupted sleep each night. Pharmacological approaches include the use of a low dose of amitriptyline (10 or 25mg a few hours before going to bed) and the cautious use of hypnotics such as zaleplon/Sonata (helpful for patients with problems initiating sleep). Anecdotal reports indicate the patients with severe sleep problems may find melatonin helpful. Advice on appropriate sleep hygiene measures should also be given. (See also section 7:3 p11).

Immunological treatments

Despite the fact that a number of immunological abnormalities have been identified in ME/CFS, there is no clear evidence about the value of immunological treatments. None of these treatments is readily available on the NHS. They should all be regarded as experimental at present, and not for routine use in ME/CFS patients.

- Ampligen, a very expensive American drug, is claimed to have both antiviral and immunomodulatory properties. Benefits have been reported in one small trial (Strayer *et al* 1994) and further assessment is currently taking place in America and Belgium. Ampligen has not yet been approved by the American FDA for use in the treatment of ME/CFS.
- Intravenous injections of immunoglobulin G have now been assessed in five RCTs. Three reported benefits (Du Bois 1986; Lloyd *et al* 1990; Rowe 1997) whereas two found no benefit (Peterson *et al* 1990; Vollmer Conna *et al* 1997). Some benefit has also been demonstrated on subgroup analysis in a small trial involving alpha interferon (See and Tilles 1996).
- Inosine pranobex/Imunovir, an immuno-modulatory drug that has a potential to enhance natural killer cell activity, is currently being assessed as a possible treatment for ME/CFS.

Irritable bowel symptomatology

This should be treated with appropriate use of bulk forming laxatives, antidiarrhoeals, antispasmodics and, if indicated, a trial involving exclusion of certain foods (*eg* wheat, citrus fruits, dairy produce) which are implicated in some cases of irritable bowel.

Muscle relaxants

Cautious use of low doses of drugs such as methocarbamol/Robaxin may be indicated in patients who complain of severe muscle spasms.

Supplements

- Significant benefits for evening primrose oil have been reported in one RCT (Behan *et al* 1994) but not in a more recently published RCT (Warren *et al* 1999). Evening primrose oil has a good safety profile and may be helpful in relieving arthralgia.
- NADH (nicotinamide adenine dinucleotide) is a natural substance which is known to trigger energy metabolism at a cellular level through ATP production. A supplement containing NADH (Enada) has been shown to be effective in one small clinical trial (Forsyth *et al* 1999).
- Carnitine deficiency has been reported as occurring in ME/CFS (Majeed *et al* 1995) and some patients claim that carnitine supplements have been helpful. One small RCT (Plioplys and Plioplys 1997) found 'statistically significant improvement' in 12 out of 18 patients taking a carnitine supplement.

Vestibular dysfunction

Vestibular sedatives such as cinnarizine/Stugeron tend to be of limited or no value in the management of dysequilibrium and other balance problems that are frequently reported by ME/CFS patients (Ash-Bernal *et al* 1995).

Vitamins and minerals

Deficiencies involving magnesium, (Cox *et al* 1991), folic acid (Jacobson *et al* 1993) and several B vitamins (Heap *et al* 1999) have been reported as occurring in ME/CFS. However, there is no evidence from clinical trials to indicate that vitamin and mineral supplementation is of value. Megadosing of vitamins and minerals can, in fact, cause serious harm. The only clear indication for supplements is in the case of women with ME/CFS who are contemplating pregnancy. They should always have their folic acid level checked and then take an appropriate folic acid supplement.

Other possible approaches

- A number of other drugs, eg selegeline/Eldepryl, amantadine/Symmetrel (Plioplys and Plioplys 1997; Bowman *et al* 1997) and methylphenidate/Ritalin in children, have been reported to be of benefit in selected ME/CFS patients. None, however, has been assessed in a clinical trial.
- A preliminary trial into the use of 5-HT3 receptor antagonists – tropisetron and ondansetron – has recently been reported from Germany (Spath *et al* 2000). Results indicate that these drugs, which are normally used to treat nausea and vomiting, and do not have dopamine antagonist properties or extrapyramidal side-effects, may be of value in ME/CFS.
- Galanthamine hydrobromide, a selective acetylcholinesterase inhibitor, has not been shown to improve fatigue or cognitive impairment in a recently completed multicentre RCT (results not as yet published).

None of these drugs can as yet be recommended for general use in ME/CFS patients.

7:3 Non-pharmacological treatments

Activity management (pacing)

This involves trying to achieve the appropriate balance between periods of activity and rest. At the onset of ME/CFS (*ie* within the first few weeks following a viral infection) a period of rest, possibly bed rest, may be necessary. Ideally, this should then be followed by a gradual increase in both physical and mental activity. It is important for patients to establish baselines at which they feel comfortable and accept that progress may be both slow and erratic. Activity levels should always be reduced during a relapse or exacerbation of symptoms.

From the doctor's point of view, this means providing clear guidance on how to set realistic goals, creating flexible plans to account for day-to-day fluctuations in energy levels and symptoms, and remaining positive about recovery. Referral to an occupational therapist or physiotherapist who can design a programme aimed at appropriate activity management can be helpful for those who are having difficulty with this crucial aspect of management.

Graded exercise regimes that involve a progressive increase in physical activity on a day-to-day basis, regardless of how a patient is coping, are not recommended as they are likely to result in a relapse.

Results from three RCTs (Wearden *et al* 1998, Powell *et al* 2001; Fulcher and White 1997) into the use of graded exercise are frequently used to claim that rest has no place in the management of ME/CFS. However, the authors of this document (Shepherd and Chaudhuri 2001), believe that appropriate periods of rest are just as important as gradually trying to increase physical and mental activity once the condition has started to stabilise.

It should also be noted that an American study (Lapp 1997) has now confirmed that inappropriate advice about exercise can easily produce a rapid and quite severe exacerbation of symptoms and that physical deconditioning does not appear to be a perpetuating factor in the illness (Bazelmans *et al* 2001).

From the medico-legal point of view, doctors who prescribe exercise programmes for ME/CFS patients must do so with just as much care as they would with a prescription drug

Management of sleep disturbance

During the early post-infectious stage of ME/CFS many patients have hypersomnia, which need not be interfered with.

Once the phase of hypersomnia starts to diminish, patients should be encouraged to adopt various simple sleep hygiene measures which should help to reduce the chance of other types of sleep disturbances developing.

- Avoid excessive amounts of caffeine-containing stimulants such as tea, coffee and cola drinks, especially during the evening.
- Afternoon sleeps should be avoided if at all possible – these should be replaced with a period of rest/relaxation if necessary.
- Try to establish a regular routine for waking up, getting up and going to bed at around the same time.
- Have a soak in a warm bath about half an hour before going to bed.
- Make sure the bed and bedroom are not too hot or too cold.

Cognitive behaviour therapy (CBT)

This approach may be helpful for a subgroup of patients with ME/CFS who are not managing their lifestyle adjustment in a satisfactory manner. CBT may also be useful for those with co-existing depression or where there are difficulties in coping socially or psychologically.

However, it should be noted that clinical trials involving the use of CBT have produced conflicting results (Deale *et al* 1997; Friedburg and Krupp 1994; Lloyd *et al* 1993; Prins *et al* 2001; Sharpe *et al* 1996) and that there are very few therapists available who have experience of dealing with this illness. CBT programmes which are based on the assumption that ME/CFS is essentially a behaviour problem perpetuated by abnormal illness beliefs and/or behaviour are unlikely to be acceptable or beneficial.

7:4 Complementary treatments

Approaches such as acupuncture and homoeopathy may be worth investigation, but patients should be advised how to find a reputable practitioner. Other alternative treatments are far more speculative. There is no evidence to support the use of widely recommended anti-candida regimes or taking megadoses of vitamins or minerals.

7:5 Other management issues

DSS benefits

The Department of Social Security makes it clear in their Disability Handbook that people with ME/CFS are as potentially disabled as those with other chronic conditions and are therefore entitled to apply for a full range of sickness and disability benefits. However, patients often have considerable difficulty in persuading examining doctors and lay adjudicators that they are genuinely ill and unable to safely care for themselves in the home.

Problems with benefit applications are often exacerbated by the way in which written and practical assessments for Incapacity Benefit and Disabled Living Allowance are badly designed for illnesses such as ME/CFS in which there are fluctuating levels of disability and ill-health. High levels of success on appeal suggest that initial applications are being refused at a higher level than is fair. The ME Association can provide patients with information on benefit applications and appeal procedures which may be relevant.

Diet and nutrition

A well-balanced diet that includes complex carbohydrates (to help stabilise blood sugar levels) and avoids caffeine should be advised. A good fluid and adequate salt intake should also be encouraged, especially for those patients who have symptoms related to hypotension.

Employment and education

A sudden return to full-time employment or education is often unrealistic. It may therefore be necessary for the GP to become involved in negotiations aimed at ensuring a more gradual or flexible return to normal activities for those who have managed to achieve a substantial degree of recovery.

Unfortunately, many people with ME/CFS are unable to return to their previous employment/educational activities or attempt to do so and find that they are unable to perform at a satisfactory level or on a sufficiently regular basis.

For those who remain severely unwell and are unable to resume employment, the possibility of early retirement on the grounds of ill health may need to be considered.

Permanent Health Insurance/Income Protection
As with state sickness benefits, some people experience considerable difficulties in successfully claiming permanent health insurance/income protection benefits – even where their inability to work is supported by statements from a GP and a reputable NHS specialist. Being in receipt of Incapacity Benefit is no guarantee that a permanent health insurance/income protection claim will be accepted. Patients who become involved in disputes involving insurance companies should be advised to contact The ME Association for detailed information on how to proceed.

Private medical sector
A wide range of investigative procedures and treatments is available from the private medical sector. These are often quite costly and their efficacy is seldom based on any reliable published evidence. Patients need to consider carefully whether such investigations and treatments will be of any genuine benefit.

Relapse or exacerbation of symptoms
Patients need to be aware of those factors which can commonly exacerbate symptoms or cause a relapse.

- Alcohol intolerance is extremely common - a factor which is recognised quickly and usually accepted.
- Intercurrent infections invariably produce a rapid deterioration and patients may well find that it then takes several weeks to return to 'normal' levels of activity.
- Immunisations appear to be capable of both triggering the syndrome as well as causing a relapse. A number of cases in health workers have followed hepatitis B vaccination. When immunisation is considered necessary, it should be arranged at a time when the patient is feeling reasonably well. Travel vaccines should not be given immediately before departure if at all possible.
- Surgery and general anaesthetics may again be unavoidable. Routine procedures should, if possible, be arranged for a time when the person is well and practical help in the home can easily be arranged for the post-operative period.
- Temperature extremes should be avoided, although a holiday in a warm sunny climate may well have its benefits.

8. Prognosis -
what are the chances of recovering from ME/CFS?

Most people with ME/CFS fall into one of four groups:

- Those who manage to return to completely normal health, even though this may take a considerable period of time. The percentage falling into this category is fairly small.
- The majority, who tend to follow a fluctuating pattern with both good and bad periods of health. Relapses or exacerbations are often precipitated by infections, operations, temperature extremes or stressful events.
- A significant minority remain severely affected and may require a great deal of practical and social support.
- Continued deterioration is unusual in ME/CFS. When this occurs, a detailed medical assessment is advisable to rule out other possible diagnoses.

Several research studies looking at prognosis in ME/CFS have now been published (Bombardier and Buchwald 1995; Hinds *et al* 1993; Sharpe *et al* 1992; Vercoulen *et al* 1996; Wilson *et al* 1994). Results from these studies indicate that ME/CFS often becomes a chronic and very disabling illness with complete recovery only occurring in a small minority of cases. The high level of debility and disability associated with ME/CFS often stems from a combination of symptoms such as fatigue, pain, sleep disturbance, cognitive impairment, and, in some cases, an associated depression.

Studies which have examined functional status and quality of life measures, (Buchwald *et al* 1996; Komaroff *et al* 1996; Schweitzer *et al* 1995) also confirm that the scale of impairment across a range of physical and mental activities can be just as great or greater than is seen in many other chronic medical conditions.

9. Severely affected patients

There are serious deficiencies in the way that severely affected ME/CFS patients (ie those who spend a considerable period of time either house, wheelchair or bed bound) are currently managed in both primary and secondary care. Although no really accurate figures are available, it is estimated that at least 25% of all people with

ME/CFS will fall into this category at some stage in their illness.

Feedback to The ME Association indicates that a great deal more could be done at a primary care level in relation to regular home assessments and investigation of new or prominent symptoms; more effective symptom control and pain management; involvement of other healthcare professionals; practical support from social services; and the availability of local respite care.

When it comes to secondary care facilities, feedback indicates that there are very few hospitals to whom severely affected patients can be referred - a situation that needs to be addressed with urgency. And even where facilities exist, more consideration needs to be given to practical problems faced by the severely affected when attending out-patient appointments. The situation is even worse in relation to the provision of suitable facilities for in-patient assessment and management.

It should also be noted that very few of the research studies into either pathoaetiology or management of ME/CFS have ever involved severely affected patients - a fact which should be borne in mind when considering the use of controversial management approaches such as CBT and/or graded exercise in this group of patients. The ME Association is currently funding the first ever study into factors which may be involved in the development of severe ME/CFS.

10. Children and adolescents

There is currently very little reliable information on the prevalence of ME/CFS among children and adolescents, but one study (Dowsett and Colby 1997) indicated that it is one of the most common reasons for long-term absence from school.

Diagnostic assessment of possible ME/CFS in this age group is very similar to that in adults. However, symptoms such as headaches and disrupted sleep patterns tend to be more prominent and there are other diagnoses (*eg* lymphoreticular malignancy, Crohn's disease) which may need to be excluded by further investigation in some instances.

Management of children and adolescents is again very similar to that of adults but with less emphasis on the use of drug treatments. Appropriate liaison with local education authorities (LEAs), schools and teachers, which is aimed at keeping education going through the use of home tutors and part-time attendance, is vital. Children who are sufficiently unwell to be away from school should generally be under the active care of a paediatrician. It should also be noted that children and adolescents with ME/CFS may be eligible for various state sickness and disability benefits.

There are a number of registered charities dealing specifically with children and adolescents with ME/CFS. Details can be obtained from The ME Association.

11. Information for patients

The ME Association provides information to patients, carers and health professionals on all aspects of ME/CFS. Information sheets are available on many of the management topics covered in this booklet.

The ME Association also recommends two self-help guides for patients:

- *Living with ME*, Dr Charles Shepherd (Vermilion, 1999).
- *ME/chronic fatigue syndrome: how to cope*, Dr Anne Macintyre (Thorsons, 1998).

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With the exception of those related to management, only key medical and scientific references are included in this booklet.

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