

# Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome: Clinical Working Case Definition, Diagnostic and Treatment Protocols

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**ABSTRACT.** Recent years have brought growing recognition of the need for clinical criteria for myalgic encephalomyelitis (ME), which is also called chronic fatigue syndrome (CFS). An Expert Subcommittee of Health Canada established the Terms of Reference, and selected an Expert Medical Consensus Panel representing treating physicians, teaching faculty and researchers. A Consensus Workshop was held on March 30 to April 1, 2001 to culminate the review process and establish consensus for a clinical working case definition, diagnostic protocols and treatment protocols. We present a systematic clinical working case definition that

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encourages a diagnosis based on characteristic patterns of symptom clusters, which reflect specific areas of pathogenesis. Diagnostic and treatment protocols, and a short overview of research are given to facilitate a comprehensive and integrated approach to this illness. Throughout this paper, "myalgic encephalomyelitis" and "chronic fatigue syndrome" are used interchangeably and this illness is referred to as "ME/CFS." [Article copies available for a fee from The Haworth Document Delivery Service: 1-800-HAWORTH. E-mail address: <getinfo@haworthpressinc.com> Website: <<http://www.HaworthPress.com>> © 2003 by The Haworth Press, Inc. All rights reserved.]

**KEYWORDS.** Clinical case definition, myalgic encephalomyelitis, chronic fatigue syndrome, ME, CFS, diagnostic protocol, treatment protocol

### INTRODUCTION

Myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) is a severe systemic, acquired illness that can be debilitating. It manifests symptoms predominantly based on neurological, immunological and endocrinological dysfunction. While the pathogenesis is suggested to be multi-factorial, the hypothesis of initiation by a viral infection has been prominent. A wide range of viruses and other infectious agents, such as Epstein-Barr Virus (1,2,3,4,5), Human Herpesvirus-6 and 7 (6,7,8,9,10), Entovirus (11,12), Cytomegalovirus (13,14,15), Lentivirus (16), Chlamydia (17), and Mycoplasma (18,19), have been investigated but findings are mixed and there is no conclusive support for any one pathogen. As antibody titers in standard laboratory tests usually employ a whole viral preparation or a single viral polypeptide, an incomplete or mutated pathogen replication could go undetected. It is unclear whether the pathogens play a direct causal role, accompany an underlying infection, trigger reactivation/replication of latent pathogens, represent reactivated latent pathogens, activate a neural response or modulate the immune system to induce ME/CFS (20). Possibly a new microbe will be identified. Viral involvement is supported by an infectious initiating trigger in at least half of the patients (21), and by confirmed findings of biochemical dysregulation of the 2-5A synthetase/ribonuclease L (RNase L) antiviral defense pathway in monocytes (22,23,24,25,26), a pathway which is activated in viral disorders (27).

Before acquiring the illness most patients were healthy, leading full and active lifestyles. ME/CFS most frequently follows an acute pro-

dromal infection, varying from upper respiratory infections, bronchitis or sinusitis, or gastroenteritis, or an acute “flu-like” illness. Other prodromal events that may stress the neuroimmunoendocrine regulatory system include immunization, anesthetics, and exposure to environmental pollutants (28), chemicals, and heavy metals (29). Physical trauma such as a motor vehicle accident, a fall, or surgery may also trigger ME/CFS. In rare occasions, ME/CFS has developed following a blood transfusion. Within days or weeks of the initiating event, patients show a progressive decline in health and develop a cascade of symptoms. The subset of patients that have a gradual onset are less likely to show discrete triggering events.

ME/CFS is primarily an endemic disorder (30,31) but occurs in both epidemic (2,32), and sporadic forms. It affects all racial/ethnic groups, is seen in all socioeconomic strata (33,34,25). Epidemiological studies have indicated a wide range of prevalence, from 75 to 2,600 per 100,000 (36,37,38,39,40,41) in different care settings; however, in a large sample of over 28,000 adults, 422 per 100,000 or 0.42% suffered from ME/CFS (36). It is more prevalent in females (522 per 100,000), as is arthritis and rheumatism. When comparing the ME/CFS prevalence figures for women with those for other illnesses, such as AIDS (12 per 100,000), breast cancer (26 per 100,000) (36), lung cancer (33 per 100,000) and diabetes (900 per 100,000), one realizes the need for a clinical definition and research for ME/CFS.

In response to cluster outbreaks of this illness, a working case definition for CFS was published under the aegis of the Centers for Disease Control (CDC), U.S.A. in 1988 (42). Their 1994 revised definition (43) has been used as the standard in Canada. These definitions, along with the 1988 and 1990 Australian definitions (30,38), and the 1991 Oxford, U.K. definition (44) have provided a basis for inter-subjective agreement and have played an essential role in orienting clinical research.

As the CDC definition was primarily created to standardize research, it may not be appropriate to use for clinical diagnoses, a purpose for which it was never intended. There has been a growing demand within the medical community for a clinical case definition for ME/CFS for the benefit of the family physician and other treating clinicians. The CDC definition, by singling out severe, prolonged fatigue as the sole major (compulsory) criterion, de-emphasized the importance of other cardinal symptoms, including post-exertional malaise, pain, sleep disturbances, and cognitive dysfunction. This makes it more difficult for the clinician to distinguish the pathological fatigue of ME/CFS from ordinary fatigue or other fatiguing illnesses.

Based on the consensus panel’s collective extensive clinical experi-

ence diagnosing and/or treating more than twenty thousand (20,000) ME/CFS patients, a working clinical case definition, that encompassed the pattern of positive signs and symptoms of ME/CFS, was developed. The objective was to provide a flexible conceptual framework for clinical diagnoses that would be inclusive enough to be useful to clinicians who are dealing with the unique symptomatic expression of individual patients and the unique context within which their illness arises. The panel felt there was a need for the criteria to encompass more symptoms in order to reflect ME/CFS as a distinct entity and distinguish it from other clinical entities that have overlapping symptoms. As fatigue is an integral part of many illnesses, the panel concurred that more of the prominent symptoms should be compulsory.

Our strategy was to group symptoms together which share a common region of pathogenesis, thus enhancing clarity and providing a focus to the clinical encounter. The inclusion of more of the potential spectrum of symptomatology in the clinical definition should allow a more adequate expression of the actual symptoms of any given patient's pathogenesis. We hope that the clinical working case definition will encourage a consideration of the ongoing interrelationships of each patient's symptoms and their coherence into a syndrome of related symptoms sharing a complex pathogenesis rather than presenting a "laundry list" of seemingly unrelated symptoms. We believe this will sharpen the distinction between ME/CFS and other medical conditions that may be confused with it in the absence of a definite laboratory test for ME/CFS.

Since the development of our clinical criteria, we have had an opportunity to review the analysis of symptoms in over 2,500 patients by De Becker et al. (45). They found that the Holmes definition (42) of fatigue, swollen/tender lymph nodes, sore throat, muscle weakness, recurrent flu-like symptoms, post-exertional fatigue, myalgia, memory disturbance, nonrestorative sleep and replacing low-grade fever with hot flashes; and the addition of ten other symptoms (attention deficit, paralysis, new sensitivities to food/drugs, cold extremities, difficulties with words, urinary frequency, muscle fasciculations, lightheadedness, exertional dyspnea and gastrointestinal disturbance) strengthen the ability to select ME/CFS patients. Based on this study, we added exertional dyspnea and muscle fasciculations to our clinical definition. All the symptoms which the De Becker et al. study (45) recommended adding to strengthen the ability to select ME/CFS patients are in our definition except paralysis, which the panel did not consider prevalent enough for inclusion in a clinical definition. The clinical definition has additional symptoms, such as orthostatic intolerance, which we feel are important in a clinical setting.

## **DIAGNOSTIC PROTOCOL**

Although it is unlikely that a single disease model will account for every case of ME/CFS, there are common clusters of symptoms that allows a clinical diagnosis.

### ***Clinical Working Case Definition of ME/CFS***

<p><i>A patient with ME/CFS will meet the criteria for fatigue, post-exertional malaise and/or fatigue, sleep dysfunction, and pain; have two or more neurological/cognitive manifestations and one or more symptoms from two of the categories of autonomic, neuroendocrine and immune manifestations; and adhere to item 7.</i></p>
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<p>1. <i>Fatigue:</i> The patient must have a significant degree of new onset, unexplained, persistent, or recurrent physical and mental fatigue that substantially reduces activity level.</p>
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<p>2. <i>Post-Exertional Malaise and/or Fatigue:</i> There is an inappropriate loss of physical and mental stamina, rapid muscular and cognitive fatigability, post exertional malaise and/or fatigue and/or pain and a tendency for other associated symptoms within the patient's cluster of symptoms to worsen. There is a pathologically slow recovery period—usually 24 hours or longer.</p>
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<p>3. <i>Sleep Dysfunction:</i>* There is unrefreshed sleep or sleep quantity or rhythm disturbances such as reversed or chaotic diurnal sleep rhythms.</p>
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<p>4. <i>Pain:</i>* There is a significant degree of myalgia. Pain can be experienced in the muscles and/or joints, and is often widespread and migratory in nature. Often there are significant <i>headaches</i> of new type, pattern or severity.</p>
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<p>5. <i>Neurological/Cognitive Manifestations:</i> <i>Two or more</i> of the following difficulties should be present: confusion, impairment of concentration and short-term memory consolidation, disorientation, difficulty with information processing, categorizing and word retrieval, and perceptual and sensory disturbances—e.g., spatial instability and disorientation and inability to focus vision. Ataxia, muscle weakness and fasciculations are common. There may be overload<sup>1</sup> phenomena: cognitive, sensory—e.g., photophobia and hypersensitivity to noise—and/or emotional overload, which may lead to “crash”<sup>2</sup> periods and/or anxiety.</p>
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6. At Least One Symptom from Two of the Following Categories:

- a. *Autonomic Manifestations:* orthostatic intolerance—neurally mediated hypotension (NMH), postural orthostatic tachycardia syndrome (POTS), delayed postural hypotension; light-headedness; extreme pallor; nausea and irritable bowel syndrome; urinary frequency and bladder dysfunction; palpitations with or without cardiac arrhythmias; exertional dyspnea.
- b. *Neuroendocrine Manifestations:* loss of homeostatic stability—subnormal body temperature and marked diurnal fluctuation, sweating episodes, recurrent feelings of feverishness and cold extremities; intolerance of extremes of heat and cold; marked weight change—*anorexia* or abnormal appetite; loss of adaptability and worsening of symptoms with stress.
- c. *Immune Manifestations:* tender lymph nodes, recurrent sore throat, recurrent flu-like symptoms, general malaise, new sensitivities to food, medications and/or chemicals.

7. *The illness persists for at least six months. It usually has a distinct onset,\*\* although it may be gradual.* Preliminary diagnosis may be possible earlier. Three months is appropriate for children.

*To be included, the symptoms must have begun or have been significantly altered after the onset of this illness. It is unlikely that a patient will suffer from all symptoms in criteria 5 and 6. The disturbances tend to form symptom clusters that may fluctuate and change over time. Children often have numerous prominent symptoms but their order of severity tends to vary from day to day. \*There is a small number of patients who have no pain or sleep dysfunction, but no other diagnosis fits except ME/CFS. A diagnosis of ME/CFS can be entertained when this group has an infectious illness type onset. \*\*Some patients have been unhealthy for other reasons prior to the onset of ME/CFS and lack detectable triggers at onset and/or have more gradual or insidious onset.*

*Exclusions:* Exclude *active* disease processes that explain most of the major symptoms of fatigue, sleep disturbance, pain, and cognitive dysfunction. It is essential to exclude certain diseases, which would be tragic to miss: Addison's disease, Cushing's Syndrome, hypothyroidism, hyperthyroidism, iron deficiency, other treatable forms of anemia, iron overload syndrome, diabetes mellitus, and cancer. It is also essential to exclude treatable sleep disorders such as upper airway resistance syndrome and obstructive or central sleep apnea; rheumatological disorders such as rheumatoid arthritis, lupus, polymyositis

and polymyalgia rheumatica; immune disorders such as AIDS; neurological disorders such as multiple sclerosis (MS), Parkinsonism, myasthenia gravis and B12 deficiency; infectious diseases such as tuberculosis, chronic hepatitis, Lyme disease, etc.; primary psychiatric disorders and substance abuse. *Exclusion of other diagnoses, which cannot be reasonably excluded by the patient's history and physical examination, is achieved by laboratory testing and imaging. If a potentially confounding medical condition is under control, then the diagnosis of ME/CFS can be entertained if patients meet the criteria otherwise.*

*Co-Morbid Entities:* Fibromyalgia Syndrome (FMS), Myofascial Pain Syndrome (MPS), Temporomandibular Joint Syndrome (TMJ), Irritable Bowel Syndrome (IBS), Interstitial Cystitis, Irritable Bladder Syndrome, Raynaud's Phenomenon, Prolapsed Mitral Valve, Depression, Migraine, Allergies, Multiple Chemical Sensitivities (MCS), Hashimoto's thyroiditis, Sicca Syndrome, etc. *Such co-morbid entities may occur in the setting of ME/CFS. Others such as IBS may precede the development of ME/CFS by many years, but then become associated with it. The same holds true for migraines and depression. Their association is thus looser than between the symptoms within the syndrome. ME/CFS and FMS often closely connect and should be considered to be "overlap syndromes."*

*Idiopathic Chronic Fatigue:* If the patient has unexplained prolonged fatigue (6 months or more) but has insufficient symptoms to meet the criteria for ME/CFS, it should be classified as idiopathic chronic fatigue.

### ***General Considerations in Applying the Clinical Case Definition to the Individual Patient***

1. *Assess Patient's Total Illness:* The diagnosis of ME/CFS is not arrived at by simply fitting a patient to a template but rather by observing and obtaining a complete description of their symptoms and interactions, as well as the total illness burden of the patient.
2. *Variability and Coherence of Symptoms:* Patients are expected to exhibit symptoms from within the symptom group as indicated, however a given patient will suffer from a cluster of symptoms often unique to him/her. The widely distributed symptoms are connected as a coherent entity through the temporal and causal relationships revealed in the history. If this coherence of symptoms is absent, the diagnosis is in doubt.

3. *Severity of Symptoms:* A symptom has significant severity if it substantially impacts (approximately a 50% reduction) on the patient's life experience and activities. In assessing severity and impact, compare the patient's activity level to their *premorbid activity level*. Establishing the severity score of symptoms is important in the diagnostic procedure (46,45), and should be repeated periodically. A chart for severity of symptoms and symptom hierarchy can be found in Appendix 3. While this numerical scale has been developed as a tool to assist the clinician and position the patient within the overall spectrum of ME/CFS severity, the severity and impact of symptoms should be confirmed by direct clinical dialogue between physician and patient over time.
4. *Symptom Severity Hierarchy:* Periodic ranking of symptom severity should be part of the ongoing evaluation of the clinical course. (Appendix 3) This hierarchy of symptom severity will vary from patient to patient and for an individual patient over time. Thus, although fatigue and post-exertional malaise are universal symptoms of ME/CFS, they may not be the most severe symptoms in the individual case, where headaches, neurocognitive difficulties, pain and sleep disturbances can dominate, at least temporarily. Establishing symptom severity and hierarchy helps orient the treatment program.
5. *Separate Secondary Symptoms and Aggravators:* It is important to try to separate the primary features of the syndrome from those that are secondary to having a poorly understood chronic illness in our society such as secondary stress, anxiety and depression and inactivity. It is also important to consider symptom interaction and dynamics, and distinguish the effects of aggravators and triggers.

### ***Discussion of Major Features of ME/CFS***

#### *Fatigue*

The *fatigue* of ME/CFS comes in many 'flavours' (47). Patients learn to recognize the difference between 'normal' and 'ME/CFS' fatigue by its qualitative flavour, its temporal characteristics and its correlation with other events and activities. The patient must have a marked degree of *unexplained, persistent or recurrent fatigue*. The fatigue should be severe enough to substantially reduce the patient's activity level, usually by approximately 50%. When considering the severity of the fatigue, it is important to compare the patient's activity level to their *premorbid activity level*. For example, a former world class athlete



could have a substantially reduced activity level and still exceed the norms for sedentary persons. Some patients may be able to do some work, but in order to do that they have had to eliminate or severely reduce other aspects of their life activities. Such interactive effects should be considered in the assessment of whether activity reduction is substantial.

*Evidence of cognitive fatiguing* should be sought in the history and may be evident during the clinical interview. Over the duration of the interview the patient's responses may become slower and less coherent. The patient may begin to have difficulty with choosing the correct words, recalling information, or become confused. Occasionally asking more than one question at a time may make the fatiguing more evident. However these changes may be quite subtle, as patients have often learned to compensate for cognitive fatigue with hyper-concentration, and have often developed strategies for taking cognitive micro-rests such as changing the subject, taking postural breaks, reducing sensory stimulation, etc. They may be quite unaware of these strategies.

#### *Post-Exertional Malaise and/or Fatigue*

The *malaise* that follows exertion is difficult to describe but is often reported to be similar to the generalized pain, discomfort and fatigue associated with the acute phase of influenza. Delayed malaise and fatigue may be associated with signs of immune activation: sore throat, lymph glandular tenderness and/or swelling, general malaise, increased pain or cognitive fog. Fatigue immediately following activity may also be associated with these signs of immune activation. Patients who develop ME/CFS often lose the natural antidepressant effect of exercise, feeling worse after exercise rather than better. Patients may have a drop in body temperature with exercise. Thus fatigue is correlated with other symptoms, often in a sequence that is unique to each patient. After relatively normal physical or intellectual exertion, a patient may take an inordinate amount of time to regain her/his pre-exertion level of function and competence. For example, a patient who has bought a few groceries may be too exhausted to unpack them until the next day. The reactive fatigue of *post-exertional malaise or lack of endurance* usually lasts 24 hours or more and is often associated with impairment of cognitive functions. There is often delayed reactivity following exertion, with the onset the next day, or even later. However, duration of symptoms also varies with the context. For example, patients who have already modified their activities to better coincide with the activity level they can

handle without becoming overly fatigued will be expected to have a shorter recovery period than those who do not pace themselves adequately.

### *Sleep Dysfunction*

Sleep and other diurnal rhythm disturbances may include early, middle or late insomnia, with reversed or irregularly irregular insomnia, hypersomnia, abnormal diurnal variation of energy levels, including reversed or chaotic diurnal rest and sleep rhythms. This results in lack of tolerance for shift work/activity or time zone shifts when travelling. Loss of the deeper phases of sleep is especially characteristic, with frequent awakenings, and loss of restorative feelings in the morning. Restless leg syndrome and periodic limb movement disorder often accompany sleep disturbance. A very small percentage of ME/CFS patients do not have sleep dysfunction, but do not fit any other disease criteria.

*Sleep Study:* It is important to rule out treatable sleep disorders such as upper airway resistance syndrome, obstructive and central sleep apnea and restless leg syndrome. *Indications:* the patient wakes up out of breath, or there is great disturbance of the bed clothes, or a sleep partner indicates that the patient snores and/or appears to stop breathing at times and/or has significant movement of her/his legs while sleeping. If poor sleep is a troublesome symptom, which does not improve with medication and sleep hygiene, it may be appropriate to have the patient assessed at a sleep clinic.

### *Pain*

Pain is often generalized and ‘nonanatomical,’ i.e., not confined to any expected structural or nerve root distribution. The pain occurs in unexpected places at unexpected times. There are pains of many qualities: sharp, shooting, burning and aching. Many patients have significant *new onset headaches* of many types, including tension and pressure headaches and migraines. There is often generalized myalgia and excessive widespread tenderness or pain that is usually perceived to originate in the muscles but is not limited to the classical FMS tender points. Patients have a lowered pain threshold or “chronic, widespread allodynia” (48) with approximately 75% of ME/CFS patients exhibiting positive FMS tender points (49). Pain may also spread from pressure on myofascial trigger points (MTP). Arthralgia without joint swelling may be

experienced but is not discriminatory for ME/CFS (45,47). A very small percentage of ME/CFS patients do not have appreciable pain, but do not fit any other disease criteria. ME/CFS should only be entertained as a diagnosis for this group when otherwise classical features follow an infectious illness, and where other diseases have been adequately ruled out.

### *Neurological/Cognitive Dysfunctions*

The neurological/cognitive symptoms are more characteristically variable than constant and often have a distinct fatiguing component to them. Especially common are cognitive ‘fog’ or confusion, slowed information processing speed, trouble with word retrieval and speaking or intermittent dyslexia, trouble with writing, reading, and mathematics, and short-term memory consolidation. There may be ease of interference from concomitant cognitive and physical activities, and sensory stimulation. It is easy to lose track of things and/or many things are forgotten: names, numbers, sentences, conversations, appointments, ones’ own intentions and plans, where things are in the house, where one has left the car, whether one has brought the car, where one is and where one is going. The memory dysfunction tends to primarily affect short-term memory. There are selective deficits in memory processing arising against a background of relatively normal cognitive functioning in ME/CFS patients. They experience more difficulty in recalling information under conditions of greater semantic structure and contextual cues, the opposite of what is found in controls and patients with other sorts of CNS impairments. They also experience difficulty maintaining attention in situations that cause them to divide their efforts, e.g., between auditory and visual channels.

*Perceptual Disturbances:* Less ability to make figure/ground distinctions, loss of depth perception or inability to focus vision and attention. One may lose portions of the visual field or one can only make sense of a small portion of it at a time. There are dimensional disturbances in timing which affect the ability to sequence actions and perceptions, and cope with complex and fast paced changes such as shift work and jet lag. Spatial instability and disorientation come in many varieties, with gait tracking problems, loss of cognitive map and inaccurate body boundaries—e.g., one bumps into the side of the doorway on trying to go through it and/or walks off the sidewalk, where the ground feels unstable.

*Motor Disturbances:* Ataxia, muscle weakness and fasciculations, loss of balance and clumsiness commonly occur. There may be an inability to automatically ‘attune’ to the environment, as in accommodating footfall to irregular ground while walking and temporary loss of basic habituated motor programs such as walking, brushing one’s teeth, making the bed and/or dialing a telephone.

*Overload phenomena* affect sensory modalities where the patient may be hypersensitive to light, sound, vibration, speed, odors, and/or mixed sensory modalities. Patients may be unable to block out background noise sufficiently to focus on conversation. There is also cognitive/informational overload—inability to multi-task, and trouble making decisions. There is emotional overload from extraneous emotional fields that unduly disturb the patient. There is motor overload—patients may become clumsy as they fatigue, and stagger and stumble as they try to walk, are not able to keep a straight line, as well as showing generalized and local weakness, and need to slow down their movements. All of these overload disturbances may form symptom clusters characteristic of the individual patient such as dizziness, numbness, tinnitus, nausea, or shooting pain. These overload phenomena may precipitate a ‘crash’ where the patient experiences a temporary period of immobilizing physical and/or mental fatigue.

#### *Autonomic Manifestations*

*Orthostatic intolerance* is commonly seen in ME/CFS patients and includes:

- *Neurally mediated hypotension (NMH):* Involves disturbances in the autonomic regulation of blood pressure and pulse. There is a precipitous drop that would be greater than 20-25 mm of mercury of systolic blood pressure upon standing, or standing motionless, with significant accompanying symptoms including lightheadedness, dizziness, visual changes, sometimes syncope, and a slow response to verbal stimuli. The patient is weak and feels an urgency to lie down.
- *Postural orthostatic tachycardia syndrome (POTS):* Excessive rapidity in the action of the heart (either an increase of over 30 beats per minute or greater than 120 beats per minute during 10 minutes of standing); and a fall in blood pressure, occurring upon standing. Symptoms include lightheadedness, dizziness, nausea, fatigue,

tremor, irregular breathing, headaches, visual changes and sweating. Syncope can but usually does not occur.

- *Delayed postural hypotension:* The drop in blood pressure occurs many minutes (usually ten or more) after the patient stands rather than upon standing.

*Tilt Test:* Further investigation by tilt test is indicated if there is a fall in blood pressure and/or excessive rapidity of heart beat upon standing, which improves when sitting or lying down. Patients often report that they experience dizziness, feeling light-headed or ‘woozy’ upon standing, or feeling faint when they stand up or are standing motionless such as in a store checkout line. Patients may exhibit pallor and mottling of the extremities. These historical symptoms and signs are sufficient for the initial diagnosis. As ME/CFS patients often have a delayed form of orthostatic intolerance, taking the blood pressure after standing may not be effective in diagnosis. Rather than having the patient stand for a period of time where there is a risk of him/her falling, we recommend using the tilt test where the patient is strapped down. The tilt test involves the patient lying horizontally on a table and then tilting the table upright to a 60°-70° angle for approximately 45 minutes during which time blood pressure and heart rate are monitored. It is recommended that orthostatic intolerance be confirmed by tilt testing prior to prescribing medication for it.

*Palpitations with or without cardiac arrhythmias* may be present. Further investigation by 24-Hour Holter Monitor may be indicated if a significant arrhythmia is suspected. Repetitively oscillating T-wave inversions and/or flat T-wave may be found. (Request to be informed of this pattern as it may not be reported or subsumed under non-specific T-wave changes by the interpreter.)

*Other common symptoms* related to ANS disturbances include breathing dysregulation—holding the breath inappropriately, irregular breathing, exertional dyspnea; intestinal irregularities and hypersensitivity to pain—irritable bowel syndrome, diarrhea, constipation, alternating diarrhea and constipation, abdominal cramps; bloating, nausea and anorexia. Bladder dysfunction and pain sensitivity can manifest as urinary frequency, dysuria, nocturia, and pain over the bladder region.

### *Neuroendocrine Manifestations*

Loss of thermostatic stability may be experienced as altered body temperature—usually subnormal and/or marked diurnal fluctuation. Hav-

ing patients take their temperature a number of times a day for a few days can confirm temperature fluctuation. It may be helpful to have patients note their activity prior to taking their temperature. Patients may have alternating feelings of hot or cold, sometimes in unusual distribution, e.g., feet are often cold, fingers may be hot, or the right side may feel hot while the left feels cold, or there may be localized feelings of heat and flushing. Many patients are intolerant of extremes in weather and experience worsening of symptoms. There are recurrent feeling of feverishness and sweating episodes. There is often a marked weight change—a reduction in some patients with loss of appetite or anorexia and a weight gain in others and an appetite that is inappropriate to their activity level.

Dysfunction of the autonomic system and hypothalamic/pituitary/adrenal axis: bodymind ‘crashing’ may lead to a general loss of adaptation to situations of overload. Excessive speed in the overloading situation or attempted response will aggravate these ‘crashes.’ Anxiety states and panic attacks may also be part of the syndrome and coherent with the other symptoms. They may not be tied to environmental events that trigger them, or they may be secondary to the symptoms. When ‘crashing,’ the patient becomes destabilized and disoriented, and thus is naturally frightened. Anxiety and panic may also appear without any external trigger. *Patients with ME/CFS have worsening of their symptoms under increased stress, and with excess physical and mental activity. They also show slow recovery.*

### *Immune Dysfunctions*

Some but not all patients exhibit symptoms coming from immune system activation, which may or may not be in response to an appropriate stimulus. For many patients this type of symptom is prominent at the acute onset stage and then diminishes or becomes recurrent as the illness becomes chronic. There is often general malaise—flu like feelings of being ‘ill’ and feeling feverish. Tender lymphadenopathy in the cervical, axillary inguinal or other regions may be present. The patient may have a recurrent sore throat with or without faucial injection. Such clinical evidence of immune system activation may occur in the absence of demonstrable viral exposure and/or be associated with inappropriate events such as physical exercise and stress. New sensitivities to food, medications and/or various chemicals are common. Patients with an acute viral onset tend to show more immune dysfunction compared to those whose onset is gradual.

### *Positive Diagnosis Using Suggestive Signs*

Faucial injection and crimson crescents may be seen in the tonsillar fossae of many patients but are not diagnostically specific. These red crescents are demarcated along the margins of both anterior pharyngeal pillars. They will assume a posterior position in the oropharynx in patients without tonsils. Oscillating or diminished pupillary accommodation responses with retention of reaction to light is also common. Cervical and axillary lymph adenopathy, often tender, may be felt. Positive fibromyalgia tender points and myofascial trigger points are common. Neurological dysfunction is often seen, including hypersensitivity to vibration sense, positive Romberg test and abnormal tandem gait. Simple mental status measures are often normal, but abnormal fatiguing on serial seven subtraction testing is common. Mutual aggravation when tandem gait and serial sevens are done simultaneously, may be evident when the baseline serial sevens test and tandem gait are both normal. As more of these signs are elicited in the same patient, the diagnosis of ME/CFS is increasingly confirmed.

There are selective deficits in memory processing arising against a background of relatively normal cognitive functioning in ME/CFS patients. The results of neurocognitive testing will depend on the focus of the test as well as many variables including the test, the milieu, schedule, pacing and duration of the test. A well controlled study (50) showed patients significantly overestimated their memory (meta memory), their performance on recall tests significantly worsened as the context increased (e.g., recognition), they made more errors when rehearsal was prevented, and had delayed mental scanning as memory load increased. Neuropsychological testing is expensive and the cost is rarely covered by provincial health plans.

### *Features of ME/CFS in Children*

Children can be diagnosed with ME/CFS if symptoms last more than three months. They tend to have numerous symptoms of similar overall severity but their hierarchy of symptom severity may vary from day to day (51). Severe, generalized pain is a common feature. Children may become dyslexic, tearful, physically weak, and exhibit exhaustion or profound mood changes. Previously active children may shun physical activity and academic standings deteriorate. They tend to do worse in mathematics and analytical subjects such as science. They are often classified as having school phobia. A British study showed that ME/CFS

was the single most common cause of *long-term* absenteeism from school in Britain (52).

### ***Clinical Evaluation of ME/CFS***

The clinical case definition provides the essential function of orientating the various aspects of the clinical encounter and forms an integral part of the whole clinical process. A clear diagnosis often has a considerable therapeutic benefit as it reduces uncertainty and orients therapy, both specific and nonspecific. Early diagnosis is important and may assist in lessening the impact of ME/CFS in some patients.

<i>Clinical Evaluation of Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome</i>
<p><i>While it is a part of the discipline of differential diagnosis to exclude alternate explanations for a patient's symptoms, it is also important to recognize the characteristic features of ME/CFS. Assess the total illness burden of the patient, taking a thorough history, physical examination and investigations as indicated to confirm clinical findings and to rule out other active disease processes. This patient evaluation is to be used in conjunction with the clinical definition. The sections on general considerations in applying the definition and the discussion of the major features give more detail.</i></p>
<ol style="list-style-type: none"> <li>1. <i>Patient History:</i> A thorough history, including a complete description of patient's symptoms as well as their severity and functional impact must be taken before attempting to classify them.           <ol style="list-style-type: none"> <li>a. <i>Focus on the Principal Symptoms of ME/CFS:</i> including fatigue, post-exertional malaise and/or fatigue, sleep dysfunction, pain, and symptoms from neurological/cognitive, autonomic, endocrine and immune manifestations. Examine the course of the symptoms, with special attention to the worsening of symptoms after exertion, prolonged recovery, and fluctuating course.</li> <li>b. <i>Presenting Complaints and Aggravating/Ameliorating Events</i> <ul style="list-style-type: none"> <li>• date of onset</li> <li>• trigger or prodromal event</li> <li>• symptoms at onset</li> <li>• progression of symptoms</li> <li>• duration of symptoms</li> </ul> </li> </ol> </li> </ol>



- hierarchy of quality and severity of current symptoms
  - symptoms which worsen with exertion; symptoms which require prolonged recovery
  - separate secondary symptoms and aggravators; consider amelioration factors
  - quantify severity of total burden of symptoms, interaction effects, and current level of physical function
- c. *Medication History*: current and past, prescribed, natural and other therapies
- d. *Sensitivities and Allergy History*: including any new sensitivities to food, medications and/or chemicals, allergies or change in status of pre-existing allergies
- e. *Past History*: earlier illnesses, exposure to environmental, residential and occupational toxins
- f. *Family History*
- g. *System Review*: many symptoms involve more than one system. Inquiry should be made for the key symptoms listed in the case definition. Careful review of the symptoms is important to exclude other conditions that may present with similar symptomatology.
- *Musculoskeletal System*: myalgia, muscle weakness, arthralgia
  - *CNS*: cognitive fatigue, fatigue and post exertional exacerbation, neurocognitive complaints, headaches, and sleep disturbances
  - *ANS & Cardiorespiratory System*: symptoms suggestive of orthostatic intolerance, neurally mediated hypotension, postural orthostatic tachycardia syndrome, delayed postural hypotension, palpitations, respiratory disturbances, vertigo, light-headedness, extreme pallor
  - *ANS & GI & GU System*: intestinal or bladder disturbances with or without irritable bowel syndrome or bladder dysfunction
  - *Neuroendocrine System*: loss of thermostatic stability, heat/cold intolerance, abnormal appetite, marked weight change, loss of sleep rhythm, loss of adaptability and tolerance for stress and slow recovery, emotional lability
  - *Immune System*: tender lymph nodes, sore throat, recurrent flu-like symptoms, general malaise

2. *Physical Examination:* An appropriate physical examination with focus on:

- a. *Musculoskeletal System:* including FMS tender point examination. There must be pain on palpation in 11 or more of the 18 designated tender point sites to meet the diagnosis of FMS (see Appendix 6). Determine if there are inflammatory changes in painful joints. Document muscle strength.
- b. *Neurological System:* a thorough neurological examination with emphasis on reflexes, tandem walk forwards and backwards, and Romberg test.
  - *Neurocognitive Symptoms:* an evaluation of cognitive symptoms including ability to remember questions, cognitive fatiguing (e.g., serial 7 subtraction) and cognitive interference (e.g., serial 7 subtraction and tandem done simultaneously).
- c. *Cardiorespiratory System:* measure lying and standing blood pressure. Arrhythmias should be noted.
- d. *Endocrine System:* check for signs of thyroid, adrenal and pituitary dysfunction.
- e. *Immune System:* most positive findings of immune system involvement in a physical examination are usually only present in the acute stage and then diminish or become recurrent. Look for tender lymphadenopathy in the cervical, axillary, inguinal regions especially early in disease, and crimson crescents in the tonsillar fossae. Examine for splenomegaly.
- f. *GI System:* check for increased bowel sounds, mild bloating and abdominal tenderness

3. *Laboratory and Investigative Protocol*

- a. *Routine Laboratory Tests:* CBC, ESR, Ca, P, Mg, blood glucose, serum electrolytes, TSH, protein electrophoresis screen, CRP, ferritin, creatinine, rheumatoid factor, antinuclear antibody, CPK and liver function, as well as routine urinalysis.

*Additional Testing:* In addition to the routine laboratory tests, additional tests should be chosen on an individual basis depending on the patient's case history, clinical evaluation, laboratory findings and risk factors for co-morbid conditions. Clinicians should carefully consider the cost/benefit ratio of any investigative test for each patient, in addition to avoiding unnecessary duplication of tests.

- b. *Further Laboratory Testing:* diurnal cortisol levels, 24 hour urine free cortisol; hormones including free testosterone, B 12 and folate levels, DHEA sulphate, 5-HIAA screen, abdominal ultrasound, stool for ova and parasites, NK cell activity, flow cytometry for lymphocyte activity, Western blot test for Lyme disease, hepatitis B and C, chest x-ray, TB skin test and HIV testing.  
Do the 37-kDa 2-5A RNase L immunoassay when it becomes available.
- c. *Differential Brain Function and Static Testing:*
- *MRI:* those with significant neurological finding should be considered for a MRI to rule out multiple sclerosis (MS), and cervical stenosis. *MRI interpretation: it is important to look for changes that are easily overlooked such as dynamic disc bulges/herniation or minor stenosis, which can be important in the pathogenesis.*
  - *Quantitative EEG, SPECT and PET Scans and Spectrography:* qEEG analysis of brain waves, SPECT estimation of dynamic brain blood flow and PET analysis of brain metabolism show diagnostic promise and will become more important as these techniques are refined and research confirms their diagnostic value.
- d. *Tilt Table Test:* if there is a fall in BP and/or excessive rapidity of heart beat upon standing; and if patient is troubled by dizziness, feeling light-headed or ‘woozy’ upon standing or when they are standing motionless. Note: fall in BP when standing may be delayed by several minutes in ME/CFS patients.
- e. *Sleep Study:* if poor sleep is troublesome and does not improve with medication or sleep hygiene. A sleep study can show poor sleep architecture, particularly the decrease in time spent in stage 4 sleep and can rule out treatable sleep dysfunctions such as sleep apnea, upper airway resistance syndrome and restless leg syndrome. Indications include: the patient wakes up out of breath, or there is great disturbance of the bedding, or sleep partner indicates that the patient snores and/or appears to stop breathing at times and/or has significant movement of their legs while sleeping.

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| <p>f. <i>24-Hour Holter Monitoring</i>: if a significant arrhythmia is suspected. Characteristic repetitively oscillating T-wave inversions and/or T-wave flats can be confirmed during 24-hour electrographic monitoring. This pattern may not be reported or subsumed under non-specific T-wave changes by interpreter.</p> <p>g. <i>Neuropsychological Testing</i>: can be utilized to identify cognitive dysfunction and/or confirm diagnosis. If done, it should focus on the abnormalities known to differentiate ME/CFS from other causes of organic brain dysfunctions.</p> |
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| <p>4. <i>Making a Positive Diagnosis for ME/CFS</i>: If the patient's presentation meets the diagnostic criteria for ME/CFS, classify the diagnosis as ME/CFS except when the specified exclusions are present. If the patient has prolonged fatigue but does not meet the criteria for ME/CFS, classify the diagnosis as idiopathic chronic fatigue.</p> |
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<p><i>New Symptoms</i>: People with ME/CFS can develop other medical problems. New symptoms need to be appropriately investigated.</p>
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### ***Differences Between ME/CFS and FMS***

ME and CFS probably are the same illness but their research definitions have emphasized different aspects of the illness. The diagnosis of myalgic encephalomyelitis and chronic fatigue syndrome are generally used interchangeably in Canada. *The clinical case definition in this document emphasizes both the lack of stamina and fatigue as well as other symptoms that support a multi-system illness, which is referred to as "ME/CFS."*

A syndrome may be delineated by means of a criterion that reflects a cutoff point on a continuum of symptoms and dysfunctions. Thus ME/CFS and fibromyalgia syndrome (FMS) can be differentiated on the basis of symptom balance in what many believe are variants of the same or similar disease pathogeneses. By criterial definition, pain is the major feature of FMS whereas post exertional malaise and fatigue are the major symptoms of ME/CFS. However the latter often involves significant cognitive dysfunction and pain, and overlap situations are common where both pain and fatigue are of similar prominence. Some FMS patients have complex symptomatology that is often indistinguishable from ME/CFS. Indeed many patients are diagnosed with both ME/CFS and FMS. Approximately 75% of ME/CFS patients also meet the criteria for FMS (49). Some patients have a syndrome pattern that changes

from one to the other. For example, FMS can evolve into ME/CFS and visa versa.

Although it may sometimes be difficult to distinguish between ME/CFS and FMS on the basis of symptomology, ME/CFS cases are commonly triggered by a viral infection, whereas physical trauma as well as other initiating events, trigger many FMS cases. Another important difference is in the response to exercise. Patients with mild FMS may be better able to tolerate aerobic exercise whereas it often aggravates the symptoms in ME/CFS patients, who may need alternate forms of exercise and a gentler progression. The possibility of overlap with ME/CFS may give rise to confusion as different situations may require different approaches to exercise.

### ***Differences Between ME/CFS and Psychiatric Disorders***

ME/CFS is *not* synonymous with depression or other psychiatric illnesses. The belief by some that they are the same has caused much confusion in the past, and inappropriate treatment.

Nonpsychotic depression (major depression and dysthymia), anxiety disorders and somatization disorders are not diagnostically exclusionary, but may cause significant symptom overlap. Careful attention to the timing and correlation of symptoms, and a search for those characteristics of the symptoms that help to differentiate between diagnoses may be informative, e.g., exercise will tend to ameliorate depression whereas excessive exercise tends to have an adverse effect on ME/CFS patients. Response to therapy directed at a presumed psychiatric entity may be a helpful distinguishing feature.

1. *Depression* may come independent of ME/CFS, or patients may feel sudden waves of depression, which just come and go erratically, and are not tied to any definite external context. These attacks are often a secondary consequence of a chronic illness. Since patients live in a depressing situation with severe social and activity restrictions at work, play and in relationships, it is not surprising that situational depression occurs in a subset of patients in reaction to their illness. These various forms of depression can often be distinguished by careful attention to the dynamics of their progression, their temporal relation to other symptoms, their degree of appropriateness, the effect of exercise, etc. Primary depression may cause a significant symptom overlap with ME/CFS, by resulting in fatigue, sleep disturbances and poor concentration.

A comparative study indicated a qualitative difference between the “depressive symptoms” of ME/CFS and those of depression (53). ME/CFS patients scored higher on items indicating physical complaints and symptoms of fatigue and they scored less frequently for disturbed mood and self-reproach than did depressed patients (53,54). In general, fatigue is not as severe in depression as in ME/CFS. Joint and muscle pains, recurrent sore throats, tender lymph nodes, various cardiopulmonary symptoms (55), pressure headaches, prolonged post-exertional fatigue, chronic orthostatic intolerance, tachycardia, irritable bowel syndrome, bladder dysfunction, sinus and upper respiratory infections, new sensitivities to food, medications and chemicals, and atopy, new premenstrual syndrome, and sudden onset are commonly seen in ME/CFS, but not in depression. ME/CFS patients have a different immunological profile (56), and are more likely to have a down-regulation of the pituitary/adrenal axis (57). Anhedonia and self-reproach symptoms are not commonly seen in ME/CFS unless a concomitant depression is also present (58). The poor concentration found in depression is not associated with a cluster of other cognitive impairments, as is common in ME/CFS. EEG brain mapping (59,60) and levels of low molecular weight RNase L (21,26) clearly distinguish ME/CFS from depression.

2. *Somatization Disorder* may also cause a symptom overlap with ME/CFS. In general, Somatization Disorder patients have a long history of complaints beginning before age 30, and don't have the sudden, discrete onset so common in ME/CFS. Usually fatigue is not so prominent a symptom, and indeed is not a criterion for the diagnosis of Somatization Disorder (which must include 4 pain symptoms, 2 GI symptoms, 1 sexual symptom and 1 pseudo-neurological symptom that cannot be explained by a general medical disorder) (58). In the DSM IV, the general category of Somatoform Disorder also includes Conversion Disorder, Pain Disorder, Hypochondriasis, Body Dysmorphic Disorder, Undifferentiated Somatoform Disorder, and Somatoform Disorder Not Otherwise Specified. The latter two subtypes have the least stringent criteria for diagnosis. Each type of disorder has special characteristics, but each also shares the general characteristics of all somatoform disorders: the presence of physical symptoms that suggest a general medical condition, but are not fully explained by any demonstrable general medical condition, by the direct effects of a substance, or by another mental disorder. As few as 5% of

ME/CFS patients meet the criteria for somatization disorder (61). There are numerous objective findings in patients with myalgic encephalomyelitis/chronic fatigue syndrome, including abnormalities in brain SPECT scans and qEEG brain topography, orthostatic intolerance and dysregulation of the 2-5A synthetase/RNase L antiviral defense pathway and low molecular weight 37kDa RNase L. These can be used to exclude somatization disorder in doubtful cases.

### ***Assessing Prognosis***

The quality of life (QOL) of ME/CFS patients show marked diminution which is more severe than in many other chronic illnesses (62,63, 64,65,66,67). ME/CFS patients were most disadvantaged in terms of vitality, recreation, social interaction, home management and work. There is a general tendency for the clinical course to plateau from between six months and six years. In a nine-year study of 177 patients, 12% of patients reported recovery (68). The patients with the least severe symptomology at the beginning of the study were the most likely to recover but there were no demographic characteristics associated with recovery. Patient with comorbid fibromyalgia syndrome demonstrated greater symptom severity and functional impairment than individuals with CFS alone (69). Other studies (70,71,72,73,37) suggest that less than 10% of patients return to premorbid levels of functioning. As the criteria become more stringent the prognosis appears to worsen (74). Chronic sleep loss [ $< 7$  hours per night] may shorten longevity (75). Infrequent deaths have been reported in the acute stage due to orthostatic cardiac irregularity (32). The chronic, incurable and poorly understood nature of this illness reduces the quality of medical and social support and may increase the risk of suicide.

The prognosis for children is better. In a 13 year follow-up of 46 children and adolescence diagnosed with chronic fatigue syndrome, 80% had satisfactory outcomes although most had mild to moderate persisting symptoms, and 20% remained ill with significant symptoms and activity limitations (76).

While statistical studies estimate group prognosis (77,78), the individual prognosis, which is highly variable, must remain a clinical estimate. To estimate individual prognosis more effectively, one must have ascertained the severity and course of the patient's illness and impairments in each of their aspects, as well as the patient's circumstances and the life-world to which they are responding. The patient's progress must

be followed over a course of time, within a therapeutic relationship. One must have tried to eliminate aggravating factors that worsen the illness and to encourage ameliorating factors. Only then can one give a reasonably adequate individual prognosis. Early diagnosis may lessen the impact of the illness. Generally, if one sees deterioration in a patient's health status over an extended time, one may expect that there would be continued deterioration, whereas if improvement was noted over an extended time period, one may hope for continued improvement. However, in the Pheley et al. study (68) there was considerable overlap of severity of illness between those who recovered and those who did not, which suggests that accurate predictions of recovery for an individual patient may not be feasible at this time. Because of the chronic nature of this illness, it is of utmost importance that further research be carried out to identify subgroups with varying prognoses.

### *Assessing Occupational Disability*

In assessing disability, physicians are called upon to assess patient symptoms, diagnosis, functional level and limitations of function as well as prognosis for recovery and treatment options. Such assessment is based on subjective reports by patients to physicians as well as objective medical evidence obtained through assessment and diagnostic testing. As third parties are likely to review the complete records of physicians, it is imperative that physicians maintain detailed, legible and comprehensive notes of the patient's history and clinical determinations made on a contemporaneous basis. Care must be taken to avoid frivolous or off-hand remarks within clinical notes as these can be construed negatively and used against a patient. Physicians should also be mindful not to deviate from their specialty areas and should ensure that patients are seen by relevant specialists.

In the context of private insurance policies, disability is defined by the degree to which there are limitations on the patients' ability to work, either in their own job or any job for which they are reasonably qualified by way of education, training and experience. With respect to Canada Pension Plan disability benefits, a person is deemed disabled and entitled to benefits when he/she is determined to have a severe and prolonged physical or mental disability by prescribed criteria. A disability is severe if by reason of the disability, the person is incapable of regularly pursuing any substantially gainful occupation. A disability is prolonged only if it is determined in a prescribed manner that the disability



**Blood Donations**

As a precautionary principle, ME/CFS patients should not donate blood as it may exacerbate symptoms. It is also possible that some patients are carrying infectious agents in their blood (27).

**RESEARCH OVERVIEW*****ME/CFS Symptoms: Description and Research Findings***

*This section is not a systematic review of research. It is a short overview indicating some of the areas of pathology being investigated. The research findings presented here are not an indication that all patients have all these dysfunctions.*

*Post-Exertional Malaise and Fatigue:* Post-exertional malaise is not only exhibited as fatigue, weakness and malaise that lasts more than twenty-four hours but also as impairment of cognitive functions. The patient takes an inordinate amount of time to regain the pre-exertional levels of function and competence. Patients may describe their malaise and fatigue as muscle exhaustion and weakness, which may be similar to that experienced with influenza. Patients have a marked degree of new onset, unexplained, persistent, or recurrent physical and mental fatigue that substantially reduces activity level.

A large study of female patients with ME/CFS showed that the patients attained almost half the maximum workload and oxygen uptake achieved by sedentary controls, as well as having elevated resting heart rates and reduced maximum heart rates (103). From this study it was suggested that sub-optimal cardiac function with inability to reach the age-predicted target heart rate seems to be a limiting factor in achieving maximal effort by ME/CFS patients, which could be due to autonomic disturbances (103). Another study indicated that the primary exercise related physiological difference in ME/CFS was a significantly lower heart rate at submaximal and maximal work level suggesting either cardiac or peripheral insufficiency (144). Therefore, “what may be an aerobic exercise regimen for healthy individuals could actually be an anaerobic activity for CFS patients” (145). Farquhar et al. (146) indicated that ME/CFS patients have significantly lower peak oxygen consumption with a trend towards lower blood volume. Significantly impaired oxygen delivery and consumption levels in muscle in patients with ME/CFS has been described (145,103).

Failing to find any statistically significant differences in maximum exercise performance between ME/CFS patients and the controls, Bazelmans et al. (147) concluded that deconditioning was not a perpetuating factor in ME/CFS. However, Lane et al. (148) showed that 32% of 96 ME/CFS patients had abnormally elevated lactate levels following a sub anaerobic threshold exercise test (SATET), and 30% of the patients had mean heart rates above those predicted. A high heart rate was as common in patients with normal lactate responses as it was in those with abnormal responses. Muscle biopsies generally did not show the changes expected as a result of inactivity (148). Patients in the subgroup with abnormal lactate responses had a significantly lower proportion of mitochondria-rich type 1 muscle fibers, but there was no evidence that this was due to a greater degree of inactivity in this subgroup (149). Exercise normally causes an increase in blood flow in the brain in a healthy individual but studies of ME/CFS patients suggest that there is a significant worsening of hypoperfusion in the temporal and frontal lobes with exercise (150,151). A small study (152) indicated that simple reaction times and movement times were longer in patients but the corticospinal inhibition appears to be normal. This suggests that the genesis of fatigue is not manifest in corticospinal output pathways abnormalities but possibly in higher control centres (152). Glucocortical deficiency is also associated with severe fatigue; however the HPA axis abnormalities are subtle, reflecting the response to stress rather than an absolute deficiency (60). Research studies suggest that low circulating blood volume and blood pooling, orthostatic intolerance and cerebral hypoperfusion may play a role in both the fatigue and post-exertional malaise (153).

Diminished heart rate and systolic and diastolic blood pressure response to stress cognitive testing were seen in ME/CFS patients compared to healthy, sedentary controls with those showing the lowest cardiovascular reactivity to cognitive stress having the highest rating of symptom severity (154). In another study by LaManca et al. (155), subjects were given four cognitive tests pre-, immediately post-, and 24 hours post-treadmill exercise to exhaustion. No differences were seen pre-exercise; however, ME/CFS patients improved at a slower rate and had a lower number of correct responses immediately post-exercise and 24 hours post-exercise than healthy controls.

*Sleep:* Most ME/CFS patients report sleep disturbance and wake up feeling unrefreshed. A few have hypersomnia and still doze during the day especially early on in the course of their illness. Sleep and other diurnal rhythm disturbances may include early, middle or late insomnia, with reversed or irregularly irregular insomnia, hypersomnia, and ab-

normal diurnal variation of energy levels, including reversed or chaotic diurnal rest and sleep rhythms.

A controlled polysomnographic study (156) suggested that ME/CFS patients have sleep initiation and sleep maintenance disturbances with significantly less stage four sleep. EEG studies suggest that this may be due to an alpha rhythm disturbance within non-REM (rapid eye movement) sleep that is accompanied by increased nocturnal vigilance and non restorative sleep (157). It has been suggested that the non-restorative nature of alpha EEG sleep may be due to suppression of nocturnal growth hormone secretion, which occurs during non-REM sleep (150). Sleep initiation difficulty has also observed in some patients (156). Interference with either the sleep-wake system or the immune system may effect the other system as evidence suggests a reciprocal relationship of the immune and sleep-wake systems (157).

*Pain:* Although the etiology of pain has not been a focus of ME/CFS research, approximately 75% of ME/CFS patients meet the criteria for fibromyalgia syndrome (49). Therefore, it is reasonable to assume that the research concerning the pain state in FMS will also apply to the pain states in ME/CFS.

Research findings suggest that the chronic pain experienced by most ME/CFS patients may be primarily a central nervous system phenomenon similar to FMS, where there is an abnormality in the brain's sensory perception and processing of pain (158), even though the onset may be related to a peripheral event. A plausible mechanism has been proposed by Bennett, by which local muscular injury can evolve into chronic generalized pain involves CNS neuroplasticity and expansion of receptive fields (159). He also suggests that the pathway involves pro-inflammatory cytokines, IL1, IL6 and TNF, activating cytokine binding sites on vagal paraganglia and causing afferent impulses to travel to the nucleus of the tractus solitarius (160). This produces cross-stimulation of the nucleus raphe magnus, which activates descending spinal tracts that sensitize second order dorsal horn neurons via a NMDA/substance P/nitric oxide cascade (160).

*Associated with Neuropathology:* A comprehensive biological model of a primary role of the central nervous system in ME/CFS is emerging. The normal coordination between the brain and the bodily systems is disrupted. It is known that the central nervous system (CNS), the autonomic nervous system (ANS), the immune system and the endocrine system interact with each other and form functional axes such as the hypothalamic-pituitary-adrenal axis (HPA) (161). Immunological abnormalities, indications of pituitary and hypothalamic involvement, ab-

normal basal plasma levels of certain neurotransmitter metabolites and cerebral perfusion abnormalities point to central nervous system involvement in ME/CFS (162).

Centrally mediated dysfunction of the hypothalamic-pituitary-adrenocortical axis appears to be associated with a cascade of autonomic and immune dysfunction features (163,164,165). In a controlled study, *SPECT* scan analysis identified significantly lower cortical/cerebellar regional cerebral blood flow (rCBF), most frequently in the frontal, parietal, temporal, occipital, and brain stem areas of the brain in 80% of 50 ME/CFS patients (166). Fischler et al. (167) failed to find marked hypoperfusion in ME/CFS patient but found asymmetry of tracer uptake at parietotemporal level. In a study by Schwartz et al. (168), *SPECT* scan abnormalities were present in 81% of patients compared to 21% of controls and there were more defects throughout the cerebral cortex in patients than controls (7.31 vs. 0.43). *PET* scans show decreased metabolism of glucose in the right mediodorsal cortex (169). All 24 ME/CFS patients in a controlled study exhibited generalized hypoperfusion of the brain with a particular pattern of decreased neuronal metabolism in the brain stem identified by *PET* scan analysis (170). These findings, which suggest significant hypoperfusion and hypometabolism in the brain stem, warrant further study (171,170). *MRI* scans suggest a higher prevalence of small white matter lesions predominantly in the frontal lobes (171). A subset of patients show cerebral atrophy, which may come from brain injury (171). In another study, punctate, subcortical areas of high signal intensity consistent with edema or demyelination was identified by *MRI* in 78% of 249 ME/CFS patients in comparison to 21% of controls (172). ME/CFS patients with *MRI* brain abnormalities reported being more physically impaired than patients without brain abnormalities (173). In a comparison of intracranial abnormalities in ME/CFS patients by *MRI* and *SPECT*, *SPECT* abnormalities appeared to correlate with clinical status, whereas *MRI* changes were irreversible (168).

*Neurocognitive Dysfunctions:* It is apparent that a primary target organ of these illnesses is the brain.

Studies suggest ME/CFS patients tend to overestimate their cognitive ability, but perform worse as the difficulty level increases (174). Numerous studies have indicated significant memory deficit in ME/CFS patients (50,175,176,177, 178). One small study suggests that patients' cognitive performance was slower but not less accurate than controls (179). Patients displayed psychomotor impairments, poor learning of information, difficulty maintaining attention and slower performance

on semantic memory and logical reasoning tasks (180). A small study (20 ME/CFS patients and 20 healthy controls) suggests impairment in spatial span, spatial working memory, pattern-location association and verbal test of unrelated word association learning and letter fluency (181). Ross et al. (182) reported that CFS patients experience more difficulty in situations that cause them to divide their efforts or rapidly re-allocate cognitive resources between auditory and visual channels. Another study (183) suggests that the global non-modality-specific attentional dysfunction is due to poor initial storage. Studies indicate that impaired memory, concentration and learning deficits are independent of signs of depression (176,177,178). ME/CFS patients demonstrate diminished cardiovascular response to cognitive stress (154) and impaired cognitive processing when they are engaged in challenging physical exertion (155). Physical and/or mental exertion exacerbate symptoms, an effect that may last for several days (184).

*qEEG topography* shows an abnormal increase in EEG activity, particularly in the slow frequency (theta) and fast frequency (beta), increased intracerebral electrical sources (gray matter), especially in the left frontal region slow frequency (delta), and fast frequency (beta) in the eyes closed condition (164,59). The left hemisphere of the brain is thought not only to be employed for language tasks and verbal thought, but also to act as a feedback system for many functions of the right hemisphere such as fine motility (60). In a study of verbal cognitive processing, which compared 46 unmedicated ME/CFS patients to 75 healthy female controls, the ME/CFS group showed reduced sources in the right hemisphere (beta), which is a consequence of interference with the left brain inhibitory regulation of the right hemisphere (59). These findings warrant further research.

*Memory:* The prefrontal cortex (PFC) helps regulate the hippocampus in new memory production. When there is dysfunction of the PFC, the hippocampus cannot function normally, as the cognitive context of each memory has not been supplied. Therefore situations may be erroneously interpreted as novel.

There are selective deficits in memory processing arising against a background of relatively normal cognitive functioning in ME/CFS patients (185). Neurophysiologically, an increase in glutamate production that occurs when nitric oxide diffuses into the pre-synaptic region of the nerve fibers will strengthen the synaptic connections, which is necessary for new memory production (186). It is plausible that the level of both glutamate and nitric oxide may be decreased in ME/CFS (150). Repetitive hippocampal neural firing during slow-wave delta sleep and

REM sleep is suggested to be necessary for short-term memory consolidation. Both may be dysfunctional in ME/CFS (118). Attentional dysfunction, difficulty in concentrating and ease of distraction result in poor initial learning and hinder memory production (187). These findings are supported by another study (188) assessing temporal demands in working memory. The overall results of this study implicate deficits in control aspects of central executive function involving more demanding tasks, requiring resistance to interference and efficient switching between processing routines (188).

*Mismanagement of Sensory Information:* Research findings suggest that there is a lower tolerance to noxious stimuli such as exposure to excessive noise, light, fast-paced and/or confusing environments in many ME/CFS patients.

Goldstein (118) proposes a plausible mechanism for the dysregulation of sensory information. *Gating* is the process whereby the prefrontal cortex (PFC) assigns relative importance to the sensory information it receives. When there is abnormal gating (for example—a high relevance may be given to insignificant distractions), there is dysregulation of the *signal to noise ratio*. Patients will experience this when they are unable to exclude background noise. The overload of noise can be fatiguing or give rise to panic attacks. A similar dysregulation also amplifies the sensory input of the olfactory system when previously tolerated foods, drugs and odors can now make one ill (118). This subset of patients usually meet the criteria for multiple chemical sensitivity (189).

*Autonomic Dysfunctions:* There are indications of a disturbance in the autonomic nervous system (190), which is responsible for regulating and stabilizing the body functions, e.g., blood pressure and body temperature fluctuate inappropriately. It has been suggested that there are low levels of the neurotransmitter glutamate, which transmits the gated information from the prefrontal cortex PFC through a neural pathway to the thalamus (118). The hypothalamus modulates the signals from the autonomic nervous system and neuroimmunoendocrine network that control pain, appetite, mood, sleep, and libido—all of which can be abnormal in ME/CFS.

*Cardiac/Circulatory Abnormalities and Neurally Mediated Hypotension (NMH):* Patients may experience a dull, pressure-like chest pain over the left breast that comes on with increasing fatigue and is not related to exertion, and they may exhibit tachycardia with minimal or no exertion, which may persist for long periods (3). One should not make the assumption that these chest pains are part of the syndrome and appropriate cardiac investigation should be carried out.

In two studies, > 95% of ME/CFS patients showed a characteristic repetitively oscillating T-wave inversions and/or T-wave flattening during 24-hour electrographic monitoring (Holter monitors) compared to abnormal readings for 22.4% of controls (191,5). Left ventricular myocardial dynamics abnormalities in the wall motion, dilation of the left ventricle and segmental wall motion were identified using a radio-isotopic gated blood pool (MUGA) in a small subset of ME/CFS patients (192). A subset of patients appears to have cardiac involvement by abortive human cytomegalovirus and/or latent Epstein-Barr herpesvirus infection (193). There appears to be simultaneous failure to inhibit synthesis of herpesvirus nonstructural gene products in the patients and herpesvirus failure to synthesize complete mature virions, which may possibly lead to non-inflammatory cardiomyopathies (193). Vagal power, a Fourier-based measure of cardiac parasympathetic activity, was computed in each four minute period of treadmill walking at 2.5 mph and in one four minute period of rest (194). ME/CFS patients had significantly less vagal power than control subjects despite there being no significant group-wise differences in mean heart rate, tidal volume, minute volume, respiratory rate, oxygen consumption or total spectrum power (194). This suggests a subtle abnormality in vagal activity to the heart (194). In a study by McCully et al. (195) the oxygen delivery to muscles was significantly reduced, and the oxidative metabolism was reduced by 20% in ME/CFS patients after exercise compared with controls. There was a significant correlation between oxidative metabolism and recovery of oxygen, which is consistent with abnormal autonomic control of blood flow (195).

*In 1995, researchers from Johns Hopkins University suggested that up to 95% of ME/CFS patients have neurally mediated hypotension, a condition in which blood pressure falls when it normally remains stable (196,197). This has resulted in a research focus on orthostatic intolerance (198,199,200), particularly in the areas of low blood volume, (153,201) abnormal sympathetic tone (202) and other autonomic nervous system dysfunctions.*

When a healthy person stands up his/her pulse rate may or may not rise slightly, but after a short time the blood pressure and pulse rate stabilize. Orthostatic intolerance can be demonstrated by taking the blood pressure first when the patient is lying down and then after standing, but the drop in blood pressure is often delayed by more than ten minutes in ME/CFS (153,203). Thus, the blood pressure of ME/CFS patients was relatively normal when prone, but they often exhibited orthostatic irregularities and aberrations when upright. Eleven of fifteen patients but

none of the controls showed an excessive reduction in systolic and diastolic BP, excessive orthostatic tachycardia, and presyncopal symptoms after standing for 60 minutes or less (153). The destabilization of blood pressure may in part be due to the loss of beat-to-beat heart rate control (202). Another study (203) showed delayed orthostatic hypotension associated with reduced pedal vein compliance during norepinephrine infusion, implying impaired sympathetic innervation of foot veins. The orthostatic venous pooling was corrected by inflation of military anti-shock trousers (MAST) to 35 mm Hg suggesting excessive lower body venous pooling. In a tilt test study of adolescents, 25/26 ME/CFS patients experienced severe orthostatic symptoms compared to 4/13 controls and 18/26 simple faint patients (202). Hemodynamic instability in ME/CFS in response to postural challenge was also noted in a controlled study by Naschitz et al. (204). Abnormal autonomic control associated with sympathetic overactivity may present as neurally mediated hypotension (198,199). Fatigue associated with low blood pressure and abnormal hemodynamic responses to upright postures can occur with or without faintness.

A low circulating erythrocyte volume, but not plasma volume, was identified in ME/CFS patients (the average was approximately 70% of normal but in some patients it was as low as 50% of normal) (153). In another small study of CFS patients by Streeten and Bell (201), 93.8% of the female patients were found to have significantly reduced red blood cell (RBC) mass, 52.6% of the patients had subnormal plasma volume, and 63.2% had below normal total blood volume. The blood vessels appear to be constricted and resist attempts to restore blood volume. This may be involved with the pathogenesis of ME/CFS and help account for the delayed hypotension and/or tachycardia caused by gravitational venous pooling (153). The reduction in circulating red blood cell mass may result in the decreased ability of the blood to carry oxygen and the reduced blood flow in the brain and thus, may contribute to the intolerance for standing and pathogenesis of ME/CFS patients (201). A subset of patients showed increased soluble fibrin monomer, elevated sonoclot rate and a moderate increase in fibrinogen levels, suggesting activation of coagulation (205). Twenty-four of thirty ME/CFS patients (80%) who had tested positive for active HHV-6 and 84% who had a hereditary abnormality, had activation of coagulation and were hypercoagulable, and thus presented a risk factor for thrombosis (206). Approximately 60% of the patients had platelet activation suggesting that fibrin deposition may lead to decreased oxygen, nutrient and cellular passage to tissues around the microcirculation with resulting systemic



compromises (205). In a study comparing morphological abnormalities in the red blood cell (RBC) population of ME/CFS patients compared to healthy controls and multiple sclerosis patients, ME/CFS patients showed the lowest percentage of normal red cells and the highest incidence of cup forms (207). These changes in the shape of the RBC may plausibly make them less flexible, thereby impairing their ability to enter the capillaries. This may reduce blood flow and delivery rate of oxygen and metabolic nutrients into the tissues, and inhibit metabolic waste from being carried away (208).

*Neuroendocrine Dysfunctions:* Several studies suggest a neuroendocrine component to the pathogenesis in ME/CFS but the exact role has not been determined. Pituitary and adrenal cortical impairments have been noted (209,210).

Several studies support a disruption of the integrity of the hypothalamic-pituitary-adrenal (HPA) axis (209,211), with reduced HPA function and enhanced 5-HT function on neuroendocrine challenge tests in ME/CFS patients (212). One study demonstrated reduced basal evening glucocorticoid levels and low 24 hour urinary free cortisol excretion, elevated basal evening adrenocorticotrophic hormone (ACTH) concentrations, and increased adrenocortical sensitivity to ACTH but a reduced maximal response (213). In an investigation of the dynamic response of the adrenal glands, there were normal basal levels of dehydroepiandrosterone (DHEA), but there was a blunted serum DHEA response curve to i.v. ACTH injection (214). Demitrack et al. (213) suggest that a mild central adrenal insufficiency secondary to a deficiency of some central stimulus to the pituitary-adrenal axis may be related to ME/CFS symptomatology. An U.K. study suggests ME/CFS patients with low cortisol have abnormally small adrenal glands (215). Significantly higher plasma prolactin concentration and increased prolactin response to buspirone may suggest changes in dopamine function (216). Attenuated prolactin responses to hypoglycemia have been reported (210). Findings by LaManca et al. (154) suggest that patients with the lowest cardiovascular reactivity to stress had the highest rating of symptom severity, which may play a role in symptoms worsening with stress.

*Immune Dysfunctions:* Brain MRI findings and lymphocyte phenotype studies, and new neurological symptoms, led Buchwald et al. (172) to suggest that ME/CFS patients may be experiencing immunologically mediated inflammatory process of the central nervous system. Immune system dysfunctions have been reviewed in the *Journal of Chronic Fatigue Syndrome* by Patarca-Montero et al. (217). Two basic regions of dysfunction have emerged. The first is immune activation as demon-

strated by elevation of activated T lymphocytes including cytotoxic T cells as well as elevations of circulating cytokines. The second is poor cellular function with low natural killer (NK) cell cytotoxicity, poor lymphocyte response to mitogenes in culture and frequent immunoglobulin deficiencies, most often IgG 1 and IgG 3 (217). No single mechanism can explain the magnitude and frequency of abnormal activity of the NK cell (218). Similar findings are supported by other studies (169,219). Compared to controls who had a greater proportion of T lymphocytes that are immunologically "naïve" (CD45RA+), ME/CFS patients have a predominance of lymphocytes with a "memory" phenotype in lymph nodes and peripheral blood (220). Decreased proportion of "naïve" cells is also seen in the peripheral blood of patients with autoimmune diseases. Immune activation is supported by findings of significantly reduced CD8 suppressor cell population and increased activation marker (CD38, HLA-DR) on CD8 cells but not in controls or patients with other diseases (221). In the Hanson et al. study (219), the only evaluated cytokine that was elevated was interleukin 4 (IL-4) suggesting a shift to a type 2 cytokine pattern. Immunopathology of reactivated latent viruses can produce subtle changes in the interactions of the HPA axis, autonomic nervous system and neuropeptides (17). Brunet et al. (222) detected delayed-type hypersensitive responses to certain common environmental antigens in 50% of ME/CFS patients, with the intensity correlating to the number of T-cells activated in vitro. Circulating plasma RNAs that have a tendency for gene rearrangement under severe physiological stress have been found to be prominent in ME/CFS patients but not found in healthy controls (223). The rearranged nucleic acids may transcribe novel proteins that may result in a tendency to degrade cellular function (223). Patients who suffered an acute onset showed significantly more dysregulation of the immune system than those patients whose onset was gradual (224).

*Antiviral Defense Pathway Dysregulation:* The identification of dysregulation of the 2-5A synthetase/RNase L antiviral defense pathway in ME/CFS patients (21,22,23,24,25,26) supports the hypothesis that viral infections play a role in the pathogenesis of this illness. When latent RNase L becomes activated by binding to ATP derived 2',5'-oligoadenylates (2-5A) produced by interferon and double stranded RNA-activated 2-5A synthetase, it inhibits the synthesis of viral (and other) proteins by cleaving single stranded RNA, thus preventing replication of viruses. The catalytic activity of activated RNase L is regulated through interaction with a specific RNase L inhibitor (RLI). ME/CFS patients have shown substantially elevated levels of RNase L and 2-5A,

a downregulation of RLI and increased presence of low molecular weight (LMW) forms of RNase L (21,22,23,24,25,26).

It has been shown that the LMW 37 kDa RNase L fragments contain ankyrin-like repeat sequences (225). Ankyrins are heterobifunctional proteins, which play fundamental roles in linking the cytoplasmic domain of integral membrane proteins to the cytoskeleton. It is suggested that the ankyrin domain containing fragments released during the pathological cleavage of RNase L in cells of ME/CFS patients are also interacting with other members of the ABC super family of proteins homologous to RLI (which is classified as a member of the ATP binding cassette (ABC) super family of ion channel membrane transporters (225,226). This could preclude their interaction with the normal cognate ankyrin protein and result in a dysregulation of their normal ion channeling function. It has been proposed that abnormalities of various ABC transporters in their ion channeling function can explain numerous symptoms of ME/CFS including altered pain sensitivity threshold, drenching night sweats, transient abnormalities in glucose metabolism, CNS abnormalities, altered immune function and reactivity, visual defects, depression, and hypersensitivity to toxic chemicals (225).

By determining the ratio of normal 80 kDa RNase L to the LMW 37 kDa RNase L found in ME/CFS patients, these patients can not only be accurately distinguished from healthy controls but also from patients with fibromyalgia syndrome and depression (21). The degree of elevation of 37 kDa RNase L correlates with the severity of symptoms (21,22,23,24,25,26).

To determine whether the LMW 37 kDa 2-5A binding protein fragments were the result of digestion by a protease such as calpain, patients' serum was checked for LMW G-actin, another calpain substrate (227). A single LMW fragment of actin was found in the serum, which correlated significantly with the presence of both G-actin and RNase L fragments in peripheral blood mononuclear cells (PBMC). The detection of LMW forms of G-actin in the serum is suggested as a useful diagnostic screen for ME/CFS as it is easy to perform. If positive, it should be confirmed by the more complicated and expensive PBMC assay for 37 kDa 2-5 A-BP (227).

*Infectious Agents:* Many research findings support the theory that ME/CFS patients commonly suffer or have suffered from a significant chronic active infection, although not all patients have changes that suggest a viral presence. It is likely that ME/CFS patients have had multiple active infections; however, it is not clear whether a given virus, mycoplasma, chlamydia, etc., plays a role in causing current symptomology,

or whether latent pathogens or antibody response to them have been re-activated due to immune system dysfunction (20).

Numerous viruses such as Epstein-Barr virus (EBV) (1,2,3,4,5), human herpesvirus-6 (HHV-6), HHV-7, and HHV-8 (6,7,8,9,10,228,229), Enterovirus (11,12), and human cytomegalovirus (HCMV) (229,27), have been implicated in subsets of patients. However, results have been mixed and inconclusive. In a group of 752 patients, 4.5% had a blood transfusion a few days to a week prior to developing acute onset ME/CFS and some had antibodies against CMV or EBV (27). In the nine patients tested, all had LMW RNase L, which accounted for the upregulation of the total RNaseL enzyme activity which is activated in viral disorders. An atypical cytomegalovirus that causes vacuolating cytopathic effects has been identified in 45/47 ME/CFS patients (13,14,15). Chlamydia has also been found in subsets of patients (229,17). Of the more than 200 ME/CFS and FMS patients tested by Nicolson et al. (230), approximately 70% tested positive for mycoplasmal infections in their white blood cells in comparison to approximately 9% of controls. More than half of these patients had double or triple mycoplasmal infections with *M. fermentans* being the most common (231). It is suggested that they target host lymphocytes causing intracellular infection. These cells can cross the blood-brain barrier and enter the spinal fluid, releasing their toxins into the central nervous system.

*Differences Between ME/CFS and Depression:* Although a subset of ME/CFS patients suffer from reactive depression secondary to the loss of their health, active life style, independent economic status and difficulty in coping with a poorly understood illness, ME/CFS is not synonymous with depression or other psychiatric illnesses.

Patients with major depression typically have elevated urinary free cortisol (UFC) excretion whereas there are significantly low levels of UFC excretion in ME/CFS patients (232). ME/CFS patients with co-morbid depression exhibited only the ME/CFS profile for UFC excretion suggesting that their depressive symptoms have a different pathophysiological basis (232). The strong inverse correlation between prolactin and cortisol responses and baseline cortisol values confirm that depression is associated with hypercortisolaemia and reduced central 5-HT neurotransmission, and suggests that ME/CFS may be associated with hypocortisolaemia and increased 5-HT function (233). ME/CFS patients show elevation of activated T lymphocytes, including cytotoxic T cells as well as elevations of circulating cytokines and low natural killer cell cytotoxicity, which are not characteristic of depression (218). Dysregulation of the 2-5A synthetase/RNase L antiviral defense path-

way and low molecular weight 37kDa RNase L found in ME/CFS patients can distinguish them from depressed patients (21). qEEG topography shows reduced sources in the right hemisphere (beta) during verbal cognitive processing in ME/CFS patients, which is a consequence of interference with the left brain inhibitory regulation of the right hemisphere. This is not a feature of depression (164). SPECT and PET scans show significant brain stem hypoperfusion and hypometabolism in ME/CFS, which is not present in depression (166,169,170). A marked reduction in red blood cell mass and circulation blood flow, and orthostatic intolerance are common in ME/CFS patients, but are not features of depression (153). The Basic Personality Inventory of ME/CFS patients is normal except for elevated pain scores (164).

### ***Future Research***

Research has now established the legitimacy of myalgic encephalomyelitis/chronic fatigue syndrome as a biological illness. In the past, lack of funding has been the major obstacle to this research. The findings showing numerous areas of organic abnormalities and the documentation of the severity of the illness should stimulate more research focus and financial support, which will hopefully attract more researchers.

Further studies need to be carried out on the basic biochemistry and biology of the illness. There is a need for more clinical trials on 'standard therapies.' A longitudinal study to determine whether a specific pattern of functional MRI abnormality, and the findings of significant hypoperfusion and hypometabolism in the brain stem and other regions of the brain warrant further study. Measuring changes in brain activity circulation patterns associated with various physical and mental activities will greatly improve the value of these observations. MRI scans of the brain and cervical spine should include foramen magnum cuts to determine the incidence of cervical stenosis or Chiari I malformation in ME/CFS patients.

Further research is needed to develop a standardized diagnostic test for ME/CFS. For example, a test that shows great potential as a blood marker is the determination of the ratio of normal 80 kDa RNase L, to the low molecular weight 37 kDa RNase L found in ME/CFS patients. This has been shown to accurately distinguish ME/CFS patients from healthy controls (21). This as well as other promising candidates for a standardized diagnostic test for ME/CFS warrant further research.

It would be helpful if research studies distinguished between mild and severe cases, and also between newly diagnosed cases and those in

chronic stages of ME/CFS. Research is usually done in isolation with various areas of foci. In order to avoid the “Blind Men and the Elephant” phenomena, it would be most helpful to have more collaborative research so that many research facets may be applied to the same patient. For example, a group of ME/CFS patients could be selected for extensive research and matched with appropriate controls. A thorough examination and a comprehensive survey of their symptoms would be completed. Various subsets of patient severity and course, type of symptoms and duration of symptoms would be compiled. They could be tested for numerous possible causative factors such as stealth virus, HHV-6, mycoplasma, etc. They could be tested for numerous biological abnormalities and the effects of various treatments. This type of study may lead to the identification of patients having one pathogenesis in common or various combinations of pathogenesis leading to different outcomes. They may indicate which subsets of patients respond best to specific treatments. This approach would be cost effective and hasten a comprehensive understanding of this complex illness. Although it is most important to keep in mind that each patient is unique and will require an individualized treatment protocol, knowing results for different subsets of patients could make the search for effective remedies more rational and efficient.

Great strides have been made in the knowledge and understanding of this illness in the last decade but there is a lot more to be done. It is hoped that the fruition of future research will bring a greater understanding of myalgic encephalomyelitis/chronic fatigue syndrome and the successful treatment of the patient.

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## NOTES

1. "Overload" refers to hypersensitivities to various types of stimuli that has changed from pre-illness status.

2. "Crash" refers to a temporary period of immobilizing physical and/or mental fatigue.

3. *Palming*: Gentle pressure from the base of both palms covering the closed eyes and held for one minute.

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