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>*

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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), Entrovirus (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

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.
1. *Fatigue:* The patient must have a significant degree of new onset, unexplained, persistent, or recurrent physical and mental fatigue that substantially reduces activity level.
2. *Post-Exertional Malaise and/or Fatigue:* 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.
3. *Sleep Dysfunction:** There is unrefreshed sleep or sleep quantity or rhythm disturbances such as reversed or chaotic diurnal sleep rhythms.
4. *Pain:** 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 *headaches* of new type, pattern or severity.
5. *Neurological/Cognitive Manifestations: Two or more* 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[1] phenomena: cognitive, sensory–e.g., photophobia and hypersensitivity to noise–and/or emotional overload, which may lead to "crash"[2] periods and/or anxiety.

6. *At Least <u>One</u> Symptom from <u>Two</u> of the Following Categories:*
   a. *Autonomic Manifestations:* orthostatic intolerance–neurally mediated hypotenstion (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 thermostatic 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 asctivity 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.

Clinical Evaluation of Myalgic Encephalomyelitis/ Chronic Fatigue Syndrome
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.
1. *Patient History:* 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. a. *Focus on the Principal Symptoms of ME/CFS:* 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. b. *Presenting Complaints and Aggravating/Ameliorating Event*s • date of onset • trigger or prodromal event • symptoms at onset • progression of symptoms • duration of symptoms

- 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 Spectography:* 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.

f. *24-Hour Holter Monitoring:* 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.
g. *Neuropsychological Testing:* 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.

4. *Making a Positive Diagnosis for ME/CFS:* 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.

New Symptoms: People with ME/CFS can develop other medical problems. New symptoms need to be appropriately investigated.

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 Gl 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

is likely to be long continued and of indefinite duration, or is likely to result in death.

Requirements of the Occupational Disability Assessment

From a medical-legal perspective, assessing occupational disability requires the physician to:

a. *Assess Symptoms of a Person's Disability:* to attempt to diagnose the condition, and most importantly to assess the duties of a person's employment and the activities of daily living. The physician is required to give a detailed and comprehensive explanation of how a person's symptoms/condition impose specific functional limitations on the person's ability to engage in the duties of their specific job, or in any job for which the person is reasonably qualified by way of education, training and experience, and which would enable the person to earn an income commensurate with that of their present job. Such an assessment should be made in the physician's clinical notes regularly, as these are the source on which third party insurers will rely most heavily.
b. *Assess Prognosis:* with respect to a person's anticipated recovery and future employability, as well as the appropriateness of rehabilitative measures. Care must be taken not to set specific deadlines or targets which cannot be met by a patient, as a patient's inability to meet a specific target as prognosed by the physician could be interpreted as malingering on the patient's part, rather than delayed recovery due to the patient's ongoing medical condition.
c. *Assess Rehabilitative Potential:* as the treating physician is in the best position to assess the patient's ongoing condition, treatment and recovery, she/he should direct and coordinate any rehabilitation efforts or other efforts to return the patient to gainful employment. Vocational rehabilitation service providers may be of assistance in this regard, but their opinions and proposals should never supplant those of the treating physician who is most directly involved in and responsible for the patient's care and well being.
d. *Provide Medical Opinion:* as to whether the severity of the patient's condition necessitates that he/she remain off work in order to effectuate a cure and/or prevent continued deterioration of the patient's condition. With respect to the impact of disability on the patient's functional limitation in employment, the physician will

be required to provide a comprehensive opinion, substantiated by detailed subjective and objective evidence.

Assessing Symptoms of Person's Disability

a. *Interviews:* Interviews are indispensable in assessing disability as they can identify cumulative effects, symptom interaction, variance in symptom severity and impact, and long range reactive exacerbation. Structured interviews should include detailed questions on symptom severity and its relation to function and circumstances. The interview can utilize the patient's diaries, questionnaires, and scales for functional assessment such as the Karnofsky Performance Scale (Appendix 10), the Medical Outcomes Study Short-Form General Health Survey (SF-36®) (65), and the Sickness Impact Profile (SIP) (79). Interviews should be repeated periodically so that "over time symptoms and impairment are assessed from many different angles" (80).
b. *Patients' Diaries and Scales:* Patient's diaries are excellent references and help the doctor assess the patient's activities of daily living, overall general functioning and degree of disability. Encourage the patient to become aware of the activities or duration of activities that cause him/her to "crash" and then use that knowledge to incorporate appropriate rest periods and pace her/himself accordingly.

    - *Symptom/Impairment Hierarchy Profile and Symptom Severity Scale:* It is helpful to have the patient fill out the symptom hierarchy/severity scale at the initial visit and every six months or so. This scale ranks symptom severity on a scale of zero to three–zero being absent and three being severe, as well as noting aggravators. Impact of symptoms on patient's lifeworld should be listed in order of decreasing severity and impact (not necessarily the same), as well as the variability of this profile both from day to day and over longer stretches of time. This is a helpful reference for monitoring the patient's progress. (Appendix 3)
    - *Daily Activities/Functional Capacity Scale:* Have the patient keep a diary of all her/his *daily activities* and *rest periods* for a one-week interval. This should include the *timing and duration* of the activities plus a rough quantification, such as specifying

type of housework performed, or walking speed, distance and terrain. Patients should rank their function level on a visual analog scale of 0 (totally bedridden)-10 (feeling great and functioning normally).

- *Sleep Diaries:* Periodically have the patient keep a one-week diary of sleep quantity and quality. A scale of 1-5 could be used, one being no sleep and 5 being good restorative sleep.

c. *Further Documentation*

- *Cardiopulmonary Exercise Testing–American Medical Association Guide for the Evaluation of Permanent Impairment:* Cardiopulmonary exercise testing (CPX) is widely used for the diagnosis and functional assessment of cardiac pulmonary and other metabolic disorders (81,82) and can be used in the diagnostic evaluation of ME/CFS. Patients can be classified into disability categories based on peak oxygen consumption levels (VO_2) using the American Medical Association's criteria for the evaluation of permanent impairment (83,84,85,86). Other data obtained from the CPX test may also be clinically useful. Heart rate and blood pressure responses during the exercise test may reveal abnormalities specific to ME/CFS including lower cardiovascular and ventilatory values at peak exercise (87). Utility of the cardiopulmonary exercise test is indicated in ME/CFS to rule out other known causes of fatigue and to determine functional capacity.
- *Computer Science and Application (CSA™) Actigraph:* In cases that need further documentation, a combination of a self-reporting scale and a CSA Actigraph is helpful. This small device is a motion detector that is capable of measuring the frequency and intensity of activity and recording values at 1-minute intervals through the day and night for up to twenty-two (22) consecutive days, thus capturing the dynamics and variability of symptoms (88). A 12-day study of 277 ME/CFS patients identified less intense and shorter activity peaks followed by longer rest periods in patients compared to controls (89).

Assessing Prognosis

See previous section (Assessing Prognosis).

Assessing Rehabilitative Potential

a. *Functional Limitations and Restrictions:* The ability of the patient to participate and function adequately in rehabilitation programs should be assessed over the long term with attention to long range cumulative effects after time spent in the program and the reactivation of symptoms. Disability can occur in the physical, cognitive and emotional realms, in various ratios of interaction and impairment. Attention should be given to:

- *Lack of Endurance Due to Physical and/or Mental Fatigue:* The patient may have profound worsening of symptoms with previously tolerated amounts of physical and mental activity.
- *Impaired Neurocognitive Functions:* Physical fatigue is often associated with loss of mental sharpness as exhibited in poor concentration, difficulty making and consolidating memories, an inability to organize tasks and increased time necessary to accomplish a task, as well as emotional disturbances reactive to the impairment. Loss of short-term memory decreases the efficiency of activity as intentions are started and forgotten and much effort is spent in locating lost articles and the constant reorganization of interrupted activities.
- *Effects of Chronic Symptoms:* Chronic pain, fatigue and errors in processing and organizing cognitive experiences have a negative impact on the patient's ability to be competitive in the work force. They affect the patient's ability to concentrate. Tasks that are tolerated for short periods of time become aggravators when the task is prolonged. Many patients have intolerance for prolonged standing, sitting or doing repetitive tasks. Stress and uncomfortable climatic conditions significantly aggravate the patient's symptoms.
- *Unpredictability of Symptom Dynamics:* Other major sources of work disability in ME/CFS are the lack of endurance, the unpredictable symptom dynamics and the presence of delayed reactive fatigue and pain and cognitive dysfunction. It usually takes a patient much longer to get going in the morning and many need frequent rests throughout the day. This prevents severely afflicted patients from taking on regularly scheduled activities, such as are typically required for work-related activities and necessary in the competitive work force.

- *Cumulative Fatigue Levels:* Assess ability to do typical repetitive actions as to duration and to the cumulative effects on fatigue levels over a longer stretch of time.

b. *Assessment by Vocational Rehabilitation Providers:* Assessment by an occupational specialist or a certified occupational therapist (OT) trained and experienced in evaluating disability may be helpful but the treating physician should direct and coordinate any rehabilitation efforts.

- *In Home Assessment:* An OT can provide valuable contextual information about daily function at home (e.g., self-care, maintenance of home, endurance, etc.). Level of function at home has direct implications for level of function in the workplace, since employment is a 24-hour issue. They can also assist the patient with energy conservation principles and in pacing their activities.
- *Workplace Assessment:* A workplace assessment provides specific information about physical, mental, emotional, social and environmental job demands. Assessment should be conducted on the job site if possible. Each job should be assessed for aggravators (Appendix 11). Many jobs can be adapted for the worker by improving ergonomics, varying job tasks and positions, and with flexibility in scheduling.

Medical Documentation and Opinion

Documentation of the severity of symptoms and disability as a part of ongoing care is recommended. The family/attending physician is in the best position to be able to directly ascertain the severity of the patient's symptoms and impact on their ability to function. Reviewing the patient's diaries can assist in assessing the impact of the symptoms on the patient's life. They can be roughly graded in the Activities of Daily Living (ADL), which are those activities directly needed for self-care such as bathing, dressing, toileting, feeding, getting in and out of bed/chairs, and walking. They will also impact the Instrumental Activities of Daily Living (IADL) which directly support the ADL such as meal preparation, shopping, housework, money management, telephone use, and travelling outside the house.

a. *Medical History:* It is important to document the total illness burden on the patient, not just that of the primary diagnosis.

- assessment by a family physician and/or a specialist conversant with ME/CFS
- diagnosis
- abnormal laboratory findings including positive findings for pathogens if available
- other objective physiological findings such as orthostatic intolerance
- *severity of symptoms and their impact on the patient's ability to function in his/her lifeworld*
- duration of illness
- response to the various treatments tried

b. *Prognosis:* The report should include an estimate of the patient's prognosis.
c. *Rehabilitative Potential and Functional Limitations and Restrictions:* The report should indicate the patient's functional limitations and restrictions and how the patient's impairments affect their ability to do ADL, IADL, function in a rehabilitative program and do work activities.
d. *Provide Medical Opinion:* The information gained through ongoing assessments, patient diaries, scales and questionnaires, etc. equips the attending physician to assess whether the patient is ready for a rehabilitation program, a slow return to work, or is disabled and unable to work due to severity of symptoms.

TREATMENT PROTOCOL

General Considerations

1. *Patient Support and Well-Being Are the Top Priorities:* Above all, one must consider and support the well-being of the patient who is embedded in the climate of confusion and uncertainty that surrounds this poorly understood chronic illness, both in the social and medical context. Begin to reduce uncertainty by establishing a positive diagnosis, reassuring continuity of care, and realistic hope based on as accurate an assessment of the patient's individual prognosis as possible.
2. *Patient Education:* Initiate education of the patient, their family and support network members as soon after the diagnosis as possible. This should include a discussion of the nature of the illness, and what