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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 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."

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

This study was aimed at monitoring of a previously suggested channelopathy in Chronic Fatigue Syndrome, and at searching for possible explanations by means of immune system characteristics. Twenty-seven CFS patients and 20 age and sex matched healthy volunteers were recruited. RNase L-ratio, percent of the norm of whole body potassium content, serum electrolytes (sodium, calcium and potassium), immune cells, blood cell count and erythrocyte sedimentation rate were determined. More than fifty percent of our patients presented with abnormal whole body potassium content. Eight patients had increased, while six had depleted potassium content. Discriminant function analysis revealed that the CFS patients and control subjects could be differentiated on immunophenotyping with the predominant cell differences being the increase in CD19+ CD5+ (mature B-) cells and the decrease in CD3− CD16+ CD56+ (NK) cells in both the percentage and count distributions. The fall in NK-cells was very strongly associated with increases in the RNase L-ratio and falls in serum calcium levels. In addition, four patients with low serum calcium levels showed lower whole body potassium levels. In conclusion, these observations suggest a channelopathy in a subset of CFS patients, probably induced by the deregulated 2-5A RNase L antiviral pathway.

KEYWORDS. Chronic fatigue syndrome, channelopathy, immunity, RNase L, potassium

Gulf War illnesses involve multiple, complex chronic signs and symptoms that loosely fit the clinical criteria for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) and/or Fibromyalgia Syndrome (FMS). Most Gulf War illness patients had multiple exposures: (a) complex chemical mixtures, including organophosphate pesticides, anti-nerve agents, carbamates and possibly nerve and blister agents, (b) radiological sources, subjecting patients to both heavy metal and radiation effects, and (c) biological sources, including bacteria and toxins and the effects of multiple vaccines. Chemically exposed patients may benefit by removing offending chemicals and depleting toxic chemicals from the patient's system and other symptomatic treatments. Patients with systemic infections, including mycoplasma and other chronic bacterial infections, can be treated with antibiotics and additional nutritional supplementation. Some patients may have their illness linked to radiological exposures, and a minority to battlefield stress. The vaccines are a prime suspect for immune dysfunction and chronic infections. The multiple, complex exposures resulted in poorly defined chronic illnesses, but subsets of Gulf War illness can be identified and effectively treated using appropriate procedures.

KEYWORDS. Gulf War Syndrome, Fibromyalgia Syndrome, Chronic Fatigue Syndrome, chemical exposures, infections, uranium, antibiotics, vaccines, chemical and biological warfare

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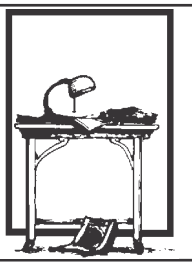

Chronic Fatigue Syndrome Guidelines

The Canadian ME/CFS guidelines in this journal are aimed at assisting healthcare professionals including medical general practitioners, specialist physicians, physiotherapists, occupational therapists, psychologists and social workers who deal with patients with abnormal fatigue states. This set of guidelines is now the third to be published, with the British (1) and Australian (2) guidelines preceding them. These clinical guidelines should not be confused with the research guidelines for ME/CFS (3-6).

The method of development of the Canadian guidelines differs from both the British and Australian guidelines principally in the manner of selecting the committee that developed them and also in the level of evidence accepted as indicating whether research findings were considered relevant. The British and Australian guidelines were developed by selected committee (the Australian committee also included a consumer representative) from within the country to develop their guidelines. The Australian guidelines committee called for submissions from interested

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parties and received at least 82 submissions. They then published draft guidelines and called for additional comments and criticisms following which they published the final guidelines. Both the British and Australian guidelines have received considerable criticism from both within the health professions and from the public. Several alternative guidelines have been suggested in trying to address the criticisms. These criticisms included claims of bias in the recommendations toward a psychiatric outcome and failure to understand the limitations of patients to perform exercise programs as well as many others.

The Canadian guidelines differ in their development as they were developed by a committee following input from invited world leaders in the research and clinical management of ME/CFS patients. The Canadian guidelines also accepted a lower level of evidence for points in their discussion and recommendations.

All three sets of guidelines are open to methodological and interpretation criticisms, however at the end of the day each is an attempt to provide what is a general guide to best practice. The Canadian guidelines represent evidence-based clinical practice guidelines developed from the best available research evidence provided by a panel of world experts. In using these guidelines the healthcare worker should also exercise their clinical judgment in evaluating the evidence in front of them and take account of individual patient preferences.

The CFS guidelines have not addressed the issue of defining the list of conditions that may result in fatigue. Thus we have chosen to give a simple overview of conditions that may result in fatigue and require to be differentiated before the diagnosis of CFS.

ABNORMAL FATIGUE (ASTHENIA)

Fatigue can be defined as a pervasive sense of tiredness or lack of energy that is not related exclusively to exertion. It should be differentiated from muscle fatigue or weakness. In most cases fatigue is usually transitory, however if fatigue is prolonged or disabling then it usually indicates a significant problem may exist. It is now generally accepted that fatigue is a very common symptom in many different conditions. There appears to be several major clinical problems associated with the diagnosis of abnormal fatigue disorders: (1) the principle diagnostic problem is determining the cause of the fatigue; (2) the clinician should not be confused that fatigue (or myalgia or the other symptoms that occur in increased frequency with fatigue) is an entity in its own right but

is a common symptom of underlying disease; and (3) to determine at what level the fatigue is clinically significant based upon determining its severity, nature and duration.

Abnormal fatigue is a common symptom reported to the clinician with rates between 10-25% of new case presentations (7-12) and thus provides a significant diagnostic challenge faced by many general practitioners. The available data on the actual biological basis for the initiation of fatigue in its multiple forms has not been established and needs to be investigated with open minds and scientific rigor, and devoid of the restrictions of the many currently accepted paradigms. The causes may be singular or co-morbid, which increases the complexity for the clinicians. Whilst knowing the exact basis for the development of a disease or symptom is not a prerequisite to development of treatment regimens, ultimately the treatments should revolve around a very thorough knowledge of the etiopathogenesis of the disease.

The different clinical groups that have investigated abnormal fatigue states have frequently made interpretations of their data based upon their restricted clinical paradigms, which are not necessarily supported if all the available scientific data had been assessed. These paradigms and biases are commonly seen in the literature for many diseases until the etiopathogenesis is established. In these days of evidence based medicine, a thorough assessment of the patient is required to avoid inappropriate diagnosis and treatment regimens.

As the primary diagnostician, the GP should be aware of the range of illnesses that require to be assessed before a diagnosis can be made. Many common yet normal life behavioral problems can induce fatigue; these include excess physical or mental activity, shift work, sleep deprivation, dietary excesses and insufficiencies, obesity, as well as prescribed and recreational drug use/abuse. Whilst these are easily identified from history taking and are usually limited in duration, many of the other causes of abnormal fatigue require additional investigation. Most of these normal life associated causes of fatigue do not last for greater than 6 months. Table 1 shows a relatively comprehensive list of these types of conditions where a combination of history, clinical examination and laboratory investigation are required to achieve the diagnosis. Some of the viral, bacterial and zoonotic infections will show a geographic distribution and not be applicable to all the readers of this journal. The clinical and diagnostic abilities of the clinician are very important in assessing these complex sets of disorders.

TABLE 1. Overview of the Potential Causes of Abnormal Fatigue

Acute or chronic infections • Viral • Bacterial • Parasitic • Zoonotic
Mood disorders
Sleep disturbances inclusive of sleep apnoea
Malignancy of any origin
Cardiovascular disorders/conditions • Agranulocytosis • Anaemia • Cardiac failure • Congenital heart disease • Cor pulmonale • Endocarditis • Subacute bacterial endocarditis • Leukaemia • Mitral stenosis • Myocarditis • Thalassaemia major or minor

Metabolic disorders/conditions
• Avitaminosis
• Diabetes mellitus
• Electrolyte disturbances
• Hyperparathyroidism
• Hypothyroidism
• Hyperthyroidism
• Euthyroid sick syndrome
• Menopause
• Metabolic disorders
  • Phenylketonuria
  • Fanconi syndrome
  • Cystic fibrosis

Endocrine disorders/conditions • Acromegaly • Addison's disease • Hypopituitarism
Connective tissue diseases • Rheumatoid arthritis • Lupus • Scleroderma
Chronic allergy reactions
Heavy metal poisoning (e.g., lead, mercury, arsenic)
Other • ME/Chronic fatigue syndrome • Cushing syndrome • Myelodysplastic syndrome • Sick building syndrome • Post-polio syndrome • Temporal arteritis • Ulcerative colitis • Malabsorption syndromes • Hodgkin's disease • Cerebrovascular accident • Head injury • Multiple sclerosis • Myasthenia gravis • Myelofibrosis • Osteomalacia and rickets • Parkinson's disease • Polycythaemia (rubra) vera • Polymyalgia rheumatica • Polyneuritis • Rheumatic fever • Cirrhosis/Uraemia

The guidelines in this edition specifically address chronic fatigue syndrome which has a specific set of diagnostic criteria not addressed in this paper.

CHANNELOPATHY

It has long been suggested that many of the symptoms seen in ME/CFS patients and similar fatigue syndromes may be associated with channelopathies. The paper by Nijs et al. assesses the association between electrolytes and immune cells, RNase L-ratio, blood cell count and erythrocyte sedimentation rate in 27 ME/CFS patients and 20 age and sex matched healthy controls. Whilst no consistent changes were found across the groups, associations were found in subsets of patients with interesting associations being found between NK-cells, the RNase L-ratio and serum calcium levels. The authors suggest that a channelopathy in a subset of CFS-patients, probably induced by the deregulated 2.5A RNase L antiviral pathway, may exist. Further studies are required into these interesting findings.

GULF WAR SYNDROME

This edition includes a comprehensive review on Gulf War Syndrome. The authors suggest that Gulf War Illnesses may involve multiple, complex chronic signs and symptoms that have a great similarity with ME/CFS and Fibromyalgia. The paper discusses the exposures to complex chemical mixtures (organophosphate pesticides, anti-nerve agents, etc.), radiological (depleted uranium) and biological agents (both primary and secondary) as well as multiple vaccines.

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Editors

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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>*

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), 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

can be expected, how to adapt to their environment, and how to develop coping strategies.

3. *Treatment Programs Should Be Individualized:* Each patient's symptoms, their dynamics and interactions, aggravators, etc., will vary and require an individualized treatment program. The symptom severity and hierarchy scales will assist in orientating therapy.
4. *Patient Participation and Empowerment:* The rules of healing differ from those of curing and must come from within. A starting point for empowerment is to validate the patients' self-experience and knowledge, as that is an integral part of their healing process.
5. *Level of Evidence of Treatment:* Many therapies used for ME/CFS have not undergone well-controlled clinical trials and may not yet be sufficiently scientifically confirmed. The level of evidence (LE) categories we have used are (90):

   I. Large double blind randomized, control trials (RCT)s, or meta-analyses of smaller RCTs, clinically relevant outcomes;
   II. Small RCTs, non-blinded RCTs, RCTs using valid surrogate markers
   III. Non-randomized controlled studies, observational (cohort) studies, case-control studies, or cross-sectional studies
   IV. Opinion of expert committees or respected authorities
   V. Expert opinion

Goal and Guidelines for Management/Treatment Programs

The *philosophy* behind management/treatment programs is of the utmost importance.

Goal

The goal of a management/treatment program is to empower the patient by encouraging them to trust their own experiences, to enhance the patients' awareness of the activities and environments in which they can cope without exacerbating symptoms and pace themselves accordingly. The program should aim at optimizing the patient's ability to maintain function in everyday activities, being as active as possible within their boundaries, and then gently extending those boundaries.

Guidelines

a. *The Treating Physician Knows the Patient Best:* The treating physician is in the best position to assess the patient's ongoing condi-

tion, treatment and recovery and is responsible for the patient's care and well-being. They should direct and coordinate treatment and rehabilitation efforts.

b. *Rehabilitation Personnel Should Be Knowledgeable About ME/CFS*

c. *The Biological Pathology of ME/CFS Must Be Respected and Reflected in the Program:*

- *The patients' total illness burden* includes the complexity of all the varied and variable dysfunctions of ME/CFS and their strongly interactive nature and expression.
- *The patients' symptoms and activity boundaries fluctuate.* They exhibit unpredictable activity rhythms in the physical, cognitive and emotional realms and lack stamina.
- *Information and sensory overload, unrealistic expectations, and inappropriate pacing* cause stress and anxiety and exacerbate the patients' symptoms.
- *The limitations of the patients' impairments/dysfunctions are a biological reality of their illness.* Patients are directly and potentially more accurately aware of their own bodies than anyone else. Early warning signs of a pending 'crash' must be respected. Patients can suffer severe and prolonged exacerbation of their illness if they transgress their activity boundaries too deeply or too often.

d. *Develop an Appropriate Adaptable Approach That Is Conducive to Healing:*

- *Assess the patient's current medical condition.* Address all dimensions of the patient's impairments and their interactive nature, as well as extenuating factors and other concerns.
- *Develop an appropriate individualized program.* The severity of impairments, the dynamics of activity boundaries, and unpredictable energy/activity rhythms differ from patient to patient and require different approaches.
- *Empower the patient* through respect. The autonomy of patients is vital to their physical and psychological health.
- *Engage the patient in establishing a program with realistic goals.* It is of utmost importance that the patients are able to set the complexity and pace of their activities, to incorporate rest intervals as needed, and control sensory exposure.
    - *Begin a program* at a level that will ensure the patient's success.

  - *Pace the program* to increase very gradually and thus ensure the patient's continued commitment and success.
  - *Develop a plan of alternate strategies* for times when the patient is having flare-ups.
- *The environment should be conducive to healing*, i.e., be at a comfortable temperature and free from confusion, bright lights and loud music or noise.
- *Directions* should be clear, simple, and concise.

Individualizing Management Programs: Lifestyle Practices and Self-Help Therapies

The experience of chronic pain, disturbed sleep and daytime fatigue may make the patient feel that his/her body, mind and lifestyle are falling apart. Whether or not a patient is able to work, lifestyle practices need to be addressed. Lifestyle/management techniques can help the patient to minimize their impairments and maximize their coping skills. Many patients address these issues with the guidance of their physician. Assessment by an occupational therapist (OT) who understands the particular problems of ME/CFS patients may be helpful for some patients. *An individualized management program may be developed with input from the patient.*

The following is an overview of components of an individualized management program and various self-help therapeutic practices. Most self-help therapies are level IV. No known therapy helps all patients but some are helpful for some patients.

1. *Patient Education:* Should include the following
   a. *Information about ME/CFS and sources of support:* The patient's meaningful others should be included in this.
   b. *Teaching patients to recognize early warning signs and prevent crashes:* Mindfulness exercises (91) encourage patients to be mindful of the impact of activities and environments on their physical, cognitive and emotional states within the ongoing flux of experience. This encourages recognition of the early warning signals of excessive fatigue and/or sensory stimulation, information overload, pressure from excessive speed, excessive stress or inability to organize tasks, etc. This provides patients with the opportunity to respect warning signs and prevent crashes, or for early treatment.

c. *Relaxation and stress reduction techniques:* including practices for centering awareness in the patients' here and now including breathing awareness (92,93), as well as various forms of meditative practices. These practices should be kept quiet and simple to encourage calmness and avoid fatigue. Both meditative and relaxation practices are useful to punctuate physical and cognitive activities with rest periods and to withdraw from excessive sensory and motor stimulation. Relax specific muscles using heat, biofeedback, stretching, and relax the muscles of the eyes by using palming.[3]

d. *Practical energy conservation information and techniques:* including self-help items that assist in the patient's daily living and functional needs such as kitchen gadgets to assist in opening jars, ways of simplifying food preparation or doing laundry and other household and garden chores, personal grooming, etc. Stretch stockings may help reduce orthostatic intolerance. Yellow sunglasses can reduce the glare of headlights during evening driving, or a sheet of thin yellow plastic placed on a page one is reading can reduce eye strain, etc.

e. *Environmental modifications:* including appropriate arrangement of furniture, lighting and heat, ergonomic considerations, organizers for paper work, proper use of reminders and simplification of tasks, e.g., bed making, laundry, cooking, bill paying, etc. They can help structure tasks and improve their consistency, and help stabilize posture and facilitate movement (94).

f. *Avoidance of specific known environmental aggravators:* to improve prognosis and prevent flare-ups of symptoms and/or further deterioration of health, it is important to avoid or minimize aggravators as much as possible. The following may be aggravators:

- viral infections
- change in sleep schedule
- cold exposure
- overexertion–physical or mental
- prolonged muscular or mental activity
- sensory overload–visual, auditory and olfactory senses
- information overload
- excessive stress
- prolonged driving

- air travel–due to jet lag, exposure to recirculating stale air and viruses, vestibular nerve stimulation and excessive vibration, etc.
- in susceptible patients, the following agents may worsen symptoms:
  - glutamate in additives, e.g., MSG
  - aspartame
  - alcohol
  - caffeine

2. *Self-Development:* Patients should be encouraged to:
   a. *Set aside a regular time for themselves:* to discover their inner feelings, needs, values, etc.
   b. *Learn to trust their inner feelings and experiences*.
   c. *Set emotional and personal boundaries:* Encourage patients to accept themselves with their limitations, get out of unfavourable situations before symptoms exceed coping powers, and learn to say "No."
   d. *Gradually extend emotional boundaries:* Develop coping skills and gradually re-expose oneself to situations that had previously given rise to anxiety and/or 'crashing.'
   e. *Extend perceptual/cognitive boundaries:* Find enjoyable activities to do on a regular basis within one's cognitive limits for fatigue such as music, painting, crossword puzzles, solitaire, exercises to improve memory (95), etc. Explore ways of gradually extending activity boundaries at their own pace.
3. *Maximizing Sleep:* Patients should be encouraged to:
   a. *Pace daytime activities appropriately to conserve energy.*
   b. *Establish a regular bedtime* and do quiet activities for an hour before bedtime.
   c. *Use bed for sleeping:* not reading, watching television or eating.
   d. *Establish a dark and quiet sleep environment:* if needed, consider eye shades and/or earplugs.
   e. *Support the body:* use a mattress and pillow that are supportive but not too hard–a contoured pillow and a pillow between the legs and under the top arm may help alleviate pain.
   f. *Consider a sleep medication* if recommended by their physician.
   g. *Keep their bedroom as a "worry free zone":* encourage patients to make a commitment to turn away from their worries when they are in their bedroom.

4. *Balanced Diet and Nutritional Considerations:* Patients should be encouraged to:
   a. *Eat at regular times*.
   b. *Eat a balanced, nutritious diet:* Patients with chronic fatiguing illnesses require a higher nutrient intake to encourage anabolic and healing processes. ME/CFS patients may be deficient in protein and essential fatty acids. Essential amino acids are required in the right balance for tissue anabolism and should come from high quality protein the diet. Diet should accommodate for individual symptoms such as those from irritable bowel syndrome. Patients should avoid foods to which they are sensitive or allergic. It is best to eat small meals more frequently and avoid processed foods and glutamate additives. Organic food is recommended if feasible, or soak produce in water with 1 tablespoon (T) of sea salt and 1 T of lemon juice per gallon for 20 minutes to help remove toxins such as pesticides.
   c. *Drink 8 to 10 glasses of water per day*.
   d. *Other nutritional considerations:*
      - *A multi-enzyme tablet with meals* may be beneficial to ensure optimal digestion and assimilation in patients who test low for digestive enzymes.
      - *Nutritional supplementation:* Each patient has a unique biochemistry and unique needs for various nutrients. The Recommended Nutrient Intake is based on estimated amounts needed to prevent overt symptoms of nutrient deficiency. It does not address optimum levels in chronic illness nor amounts required to support the healing process. Nutrient bioavailability has sometimes not been considered, e.g., some nutrients work synergistically, so if one is missing, the body may not be able to use others properly.

        When practical, a vitamin profile with levels of vitamins A, E, B complex and C can be helpful to ensure that proper nutritional supplements are prescribed. The principles and vitamin supplementation strategy of Travell, Simons et al. (96) have been found to be useful. High levels of fat-soluble vitamins such as vitamins A and E can cause toxicity that is difficult to remedy. It is important not to prescribe them in excessive dose. Excess vitamin A can lead to nightshade toxicity and contribute to musculoskeletal pain (97). If a vi-

tamin profile has not been obtained, a patient may start with a good one-a-day vitamin/mineral supplement. Replenishing electrolytes may be helpful. Try adding extra antioxidants such as vitamins E and C, olive leaf extract, and alpha-lipoic acid. Add one supplement or a synergetic group one at a time, and test it for three months for effectiveness.

- Many other nutritional, vitamin and mineral supplements, herbal remedies, etc., have been tried, but it is hard to separate their specific effects from their general effects of assisting the patient coping powers.

5. *Appropriate Body Movement and Fitness:* Patients should be encouraged to:
   a. *Establish habits of good body mechanics* for sitting, driving, lifting, etc.
   b. *Improve balance and orientation* and lessen visual spatial stabilization (98,99) (Appendix 9).
   c. *Stay as active in their daily activities* as they can to maintain strength.
   d. *Avoid house and yard work beyond their capacity*.
   e. *Maintain an appropriate exercise program*. (See following section.)

Do not misuse a tolerable day!

Dr. Robert Olin, Karolinska Institute, Sweden

Individualizing ME/CFS Exercise Programs

As much care must be taken in prescribing exercise as in prescribing medications to ME/CFS patients (100). Exercise programs must be entered cautiously as clinical studies have indicated that symptoms worsened in approximated half of the ME/CFS patients (100,101). Exercise programs should adhere to the previous stated goals and guidelines and be limited to non-fatigue exercise. Jones and Clark (102), exercise physiologists, have developed guidelines for exercise programs for fibromyalgia syndrome. As up to 75% of ME/CFS patients meet the criteria for FMS (49) this program would also be appropriate for ME/CFS. We have summarized Jones' and Clark's suggestions and adapted them for ME/CFS. Patients with ME/CFS usually have less tolerance for exercise than do those patients who have FMS alone.

1. *Initial Patient Evaluation:* Prior to prescribing exercise, it is important to assess the patient's history and physical condition with special attention to *cardiac function*. ME/CFS patients may have elevated resting cardiac function and reduced maximum heart rates, with an inability to reach predicted target heart rates (103). *Pain generators and risk factors must be identified* and include prior injuries, painful myofascial trigger points, osteoarthritis in weight bearing joints, risk for adverse cardiac events during exercise, balance problems, orthostatic intolerance and post-exertional fatigue, problems with eccentric muscle work, medication that may have a positive or negative effect, current level of fitness, etc.
2. *Optimize Medical Management Before Introducing an Exercise Program:* Patients whose fatigue, pain and concomitant conditions are under control may benefit from mild non-fatiguing exercise. Beginning an exercise program too early lessens the likelihood of the patient succeeding. Exercise is not recommended for some patients.
3. *Principles of Treatment:* The professional must be knowledgeable about ME/CFS and utilize the following principles:
    a. *Minimize Muscle Microtrauma:* The most important factor in keeping the patient active is to start with low intensity exercise and minimize movements which produce eccentric muscle contractions (the muscle contracts while being elongated) such as overhead movements.
    b. *Minimize Central Sensitization:* Activities that would be considered trivial to a healthy person can cause pain and injury in the ME/CFS patient. Help the patient find the right level of intensity of exercise to allow him/her to be as active as possible without causing flare-ups. Note: Many ME/CFS patients have reduced maximum heart rates (103), possibly due to autonomic disturbances, and should not be pushed towards age-predicted target heart rates.
    c. *Maximize Self-Efficacy:* In order to successfully engage and maintain patients in an exercise program, they must have a sense of autonomy. This is particularly important for the ME/CFS patient who has usually lost the natural antidepressant effect of exercise and experiences post-exertional malaise and/or fatigue. Limit exercises to those that do not cause significant pain. Gradually (over months) increase the program by fre-

quency and the duration of exercise periods if tolerated, but the level of intensity should be kept low.

4. *Write an Individualized Exercise Program in Conjunction with the Patient:* Allow the patient to express his/her concerns and expectations. Exercise programs must be adapted to accommodate the patient's circumstances and needs. Those patients who are more impaired and not able to tolerate an exercise program should be encouraged to increase physical activity within their limits. Help patients choose activities they find enjoyable. Thorough evaluations and follow-up visits are necessary in order to establish the optimum program for an individual. Programs should include the following components, but they do not need to be done consecutively.
   a. *Warm-Up and Warm-Down Periods:* are important to prevent injury.
   b. *Strength Training:* builds up muscles and stabilizes joints, improves general health and the ability to do activities of daily living. The focus is on muscle toning and functional strength and should include exercises to improve the strength of the upper and lower body, abdominal and paraspinal areas. As there may be a delay in the muscles' return to a resting state following contraction (102), take four counts to move the muscle into a contracted position, two counts to relax the muscle, and then a four-count pause between repetitions. For example, biceps– begin with arm resting on leg or chair arm, move hand to shoulder (4 counts), return arm to starting position (2 counts) and relax (4 counts). Movements should be kept on a parallel plane. Overhead movements should be confined to gentle stretching but patients should avoid overhead strength and endurance training. Small abdominal crunches, being careful to support but not pull head or neck, help strengthen abdominal muscles, but sit-ups should be avoided.
   c. *Endurance Conditioning:* should consist of non-impact loading exercises. Have the patient find activities that they find enjoyable such as walking or gentle acquasize in a heated pool. For those patients who are limited in their ability to walk, exercise can be done while sitting on a chair.
   d. *Flexibility:* stretching performed properly can relieve pain in tightened muscle bands. Muscles should be warmed prior to stretching. Holding a stretch at the point of resistance will "allow the Golgi tendon apparatus to signal the muscle fibers to

relax" (102). Avoid stretching muscles to the point of pain, as that will cause additional fibers to contract.

e. *Balance:* alterations in sensory and motor functions can affect balance. As many ME/CFS patients have NMH or POTS, extra care should be taken in this area. Before exercising, these patients should drink water with a little salt and be well hydrated. Help patient establish their "center" (see Appendix 9). Light intensity and muscle strengthening exercises can improve balance.

f. *Pacing:* it is most important that the ME/CFS patient has a sense of control over the pacing of their program. This will increase the likelihood of success and continued commitment. Begin with three two-minute sessions three times weekly, and gradually increase to the three ten-minute or two fifteen-minute sessions if tolerated. Patients will vary as to what and how much they can do. Optimally, the goal is to gradually build up an *accumulation* (102,104) of thirty minutes of exercise/activity on most but not all days. For example, the patient could do a 10 minute stretching routine in the morning, a ten minute strengthening routine at noon and go for a 10 minute walk in the afternoon. Decrease the time and intensity of the exercises/activities on bad days but do not overdo it on good days. Patients should end their exercise programs feeling that they could have done a little more (102). Some patients cannot reach the optimum level and should just be as active as they can within their limitations.

5. *Cautions Regarding Exercise/Rehabilitation Programs:*

   a. Programs designed for mechanical disorders such as back injuries may not be appropriate for ME/CFS patients.
   b. Externally imposed programs may not respect the patient's autonomy and impede self-direction. Most patients are well motivated to improve their condition and have lost much more than they could possibly ever gain from becoming ill. We must be very careful concerning any program that presupposes that patients are merely wrongheaded about their illness and activity limits.

Cognitive Behavior Therapy (CBT) and Graded Exercise Therapy (GET)

Two hypotheses have been presented as underlying the CBT model of chronic fatigue syndrome (105). The first hypothesis "assumes that

the pathophysiology of CFS is largely irreversible, but considers that a fine-tuning of the patient's understanding and coping behavior may achieve some improvement in his or her quality of life." The second hypothesis is based on the premise that the patient's impairments are learned due to wrong thinking, and "considers the pathophysiology of CFS to be entirely reversible and perpetuated only by the interaction of cognition, behavior, and emotional processes. According to this model, CBT should not only improve the quality of the patient's life, but could be potentially curative" (105). Some proponents suggest that "ideally general practitioners should diagnose CFS and refer patients to a psychotherapist for CBT without detours to medical specialists as in other functional somatic syndromes" (106,107).

The first hypothesis seems reasonable within the multi causal biopsychosocial model of disease and illness, however a cure may be found. But there is much that is objectionable in the very value-laden second hypothesis, with its implied primary causal role of cognitive, behavioral and emotional processes in the genesis of ME/CFS. This hypothesis is far from being confirmed, either on the basis of research findings or from its empirical results. Nevertheless, the assumption of its truth by some has been used to influence attitudes and decisions within the medical community and the general cultural and social milieu of ME/CFS. To ignore the demonstrated biological pathology of this illness, to disregard the patient's autonomy and experience and tell them to ignore their symptoms, all too often leads to blaming patients for their illness and withholding medical support and treatment.

It is unlikely that the CBT and GET studies that were included in the recent review of treatments (108) dealt with comparable homogeneous groups since different inclusion and exclusion criteria were used in selecting the test patients and control groups. For example, in the Prins et al. (106) CBT study on ME/CFS, patients had to meet the CDC criteria "with the exception of the criterion requiring four of eight additional symptoms to be present." If the sole CDC criterion that patients had to meet was prolonged fatigue, is not this study on chronic fatigue, rather than ME/CFS? In a study by Fulcher and White (109), comparing graded aerobic exercise to flexibility therapy, ME/CFS patients who had an appreciable sleep disturbance were excluded because of the effect that poor sleep has on fatigue. This is puzzling as in a study of symptom prevalence and severity by De Becker et al. (45), 94.8% of 951 patients meeting the Holmes criteria, and 91.9% of 1,578 patients meeting the Fukuda criteria, reported sleep disturbance with an average severity of 2.5 and 2.4, respectively, out of 3. When sleep disturbance is

such an integral part of ME/CFS, do the findings in the Fulcher and White study (109) apply to ME/CFS?

A systematic review of prognosis studies show that the less stringent the clinical criteria, the better the prognosis (74). In two of the studies reviewed (110,37), 22% and 26% of patients with chronic fatigue reported recovery, respectively, whereas none and 6% of the ME/CFS patients recovered from fatigue. Therefore, care must be taken not to classify patients experiencing chronic fatigue as ME/CFS patients unless they meet *all the criteria* for ME/CFS, as the outcomes for these two patient groups are substantially different. It is interesting to note that in the treatment review (108), all the CBT and GET studies that indicated improvement used the less restrictive Oxford criteria with the exception of the Prins study (106) that used the CDC criteria for prolonged fatigue but eliminated the other CDC criteria. All studies excluded ME/CFS patients who were too ill to regularly attend treatment sessions.

The complexity of CBT studies, their varied inclusion and exclusion criteria, the very limited portions that can be properly blinded, and the subjective means used for most evaluations, puts in question the validity of their results. In addition, the numerous variables between the CBT studies, the CBTs and control programs, the different comparison therapies, and the varied frequency and duration of therapy, make it very challenging to determine which parts are responsible for any perceived improvement. Are any effects due to the shift in cognitive beliefs, the exercise involved, the amount and quality of the attention and counseling, the discontinuance of other medical therapies during the test period, etc.? Thus the Powell et al. study (111) found GET alone to be as effective as CBT, and the Risdale et al. study (112) found CBT to be no more effective than counseling.

The GETs included in the review (108) generally involved graded aerobic activities with variable amounts of supervision. These three studies (109,111,113) showed positive effects but the results were modest. Although the more carefully supervised study of Fulcher and White (109) found that 55% of the patients improved over a three month period compared to 27% of patients given flexibility and relaxation exercises, the most common result in both groups was "feeling a little better." Since "graded aerobic exercises programs can help reduce incapacity and symptoms in many chronic and painful conditions" (109), one wonders about the specificity of any effects in ME/CFS patients.

Do study results represent a true reflection of the ME/CFS population when there is a high dropout rate? The Prins et al. study (106) on

CBT reported significant improvement in fatigue severity in 35% (20 of 58) of the patients. However, these figures do not reflect that 26% (99 of 377) of the patients who were eligible for the study "refused to take part," and of the 93 patients who were assigned to CBT, 41% (38) did not complete the trial. In a British study (100), 1,214 of 2,338 patients had tried graded exercise. Of these 417 found it to be helpful, 197 reported no change and 610 (50%) indicated that it made their condition worse. This was the highest negative rating of any of the pharmacological, non-pharmacological and alternate approaches of management covered in the questionnaire and may help explain the high drop out rates noted in some of these programs.

The question arises whether a formal CBT or GET program adds anything to what is available in the ordinary medical setting. A well informed physician empowers the patient by respecting their experiences, counsels the patients in coping strategies, and helps them achieve optimal exercise and activity levels within their limits in a common sense, non-ideological manner, which is not tied to deadlines or other hidden agenda.

Physicians must take as much care in prescribing appropriate exercise as in prescribing medications to ME/CFS patients (100). Attending physicians should only approve of exercise programs in which the patient's autonomy is respected, appropriate pacing is encouraged, fluctuations in severity of symptoms are taken into account, and adequate rest periods are incorporated. Patients should be monitored frequently but unobtrusively for signs of relapse.

Treatment of Symptoms Causing Major Impairment and Those Causing or Aggravating Other Symptoms

NOTE
This treatment section is NOT a systematic review of available treatments. This is an overview of some of the medications, which members of the panel have found useful for some patients in their clinical practice.

Therapeutic Principles

1. *Keep the therapeutic regimen as safe, simple, effective and inexpensive as possible.*

2. *Many patients with ME/CFS are hypersensitive to medications given in the usual doses. Always start at a lower dose than recommended and gradually build up, to determine tolerability. Add or subtract remedies one at a time, and give remedies enough time to show their effects, and exclude non-specific 'placebo' effects (approximately three months). Keep testing them to see if they are still necessary. Be careful of the addictive potential of benzodiazepines for some patients.*
3. *The plethora of these remedies shows that none are universally effective. Many remedies help a few patients to varying degrees, but none help all of them. There is no clear specific treatment. It is still a matter of trial and error to find effective remedies. The primary therapeutic goal of lifestyle adjustment–to determine that with which the patient can cope without aggravating her/his symptoms–remains of paramount importance, and should not be neglected in the search for remedies.*

There is no known cure for ME/CFS; however, the physician is usually able to help reduce the severity of the patient's symptomology. Many of the recommendations and therapies have not been subjected to controlled clinical trials or may not have been scientifically confirmed. However, there is some scientific basis and/or recommendations of experts in the field with clinical experience that justifies their inclusion. They are worth pursuing in the individual patient as long as they are safe and their side effects remain acceptable. Their values for groups may be confirmed in the future. Always advise patients of possible side effects.

The primary source of information for the tables concerning more common and important side effects and levels of evidence is the clinical experience of the expert panel members. This has been supplemented by information from the *Compendium of Pharmaceuticals and Specialties*, 36 edition 2001, Canadian Pharmacist's Association; <www.intilihealth.com> for new drugs; *Herbs: Everyday Reference for Health Professionals*, editor in chief, Frank Chandler, 2000, Canadian Pharmacist Association and Canadian Medical Association; and individual references as indicated.

The panel ranked the following pharmaceuticals in rough order, taking into account the number of members of the panel favoring the pharmaceutical and their variance. Different patients are helped by different pharmaceuticals.

1. *Sleep Disturbance:* Consider both the sleep quantity and its restorative quality.

   Physical Remedies: Treat associated sleep problems, e.g., positive pressure mask for sleep apnea. Sleep hygiene, relaxation techniques and supportive cervical pillows can be helpful.

   Other Remedies: Level of evidence–V: Melatonin: 1-3 mg qhs, valerian: 400-900 mg of the standardized extract orally qhs, calcium and magnesium salts such as the citrate or gluconate: 200-500 mg of qhs in a 2 to 1 ratio, or aromatherapy at bedtime.

Pharmaceuticals for Sleep Disturbance			
NOTE: "LE" in last column stands for "level of evidence"			
Drug	**Dose**	**Effect/Comments**	**LE**
Amitriptyline	5-10 mg qhs to start; gradually increase by 10 mg qhs until optimal effect (20-50 mg)	Tricyclic antidepressant. Often effective for sleep in the *short term. Warn about possible weight gain. Side effects can be severe even at low dose*–especially early morning grogginess and confusion, dry mouth, increased appetite, constipation, urinary retention, blurred vision, palpitations, hypotension. Reassess patient periodically. Side-effects are often dose related and if tolerated, tend to decrease with time. Benefits are usually seen 2-4 weeks after initiation. *Do not use in the presence of MAO inhibitors. Tricyclics may enhance the effects of alcohol and other CNS depressants.*	IV
Zopiclone	3.75-7.5 mg qhs	It may increase amount of stage III and IV sleep. Effect lasts up to 7 hours. Side effects to watch for include excessive drowsiness and incoordination.	IV
Trazodone	25-100 mg qhs	Tetracyclic sedative and antidepressant. It increases the depth and quality of sleep. Common side effects include excessive drowsiness, nausea, headache and dry mouth. Also watch for less common manifestations of CNS depression, cardiac arrhythmias and postural hypotension, constipation, urinary retention, priapism and allergic manifestations. Precautions are similar to those for tricyclics.	IV

Drug	Dose	Effect/Comments	LE
Doxepin	2-20 mg qhs	Tricyclic antidepressant. Start low and gradually increase the dosage as tolerated. It is slower acting, but helps to keep patient asleep longer. Side effects and precautions are similar to those for amitriptyline.	IV
Clonazepam	0.5-2 mg qhs	A benzodiazepine. It has an intermediate onset of action (1-3 hours) for sleep induction, and also has anxiolytic and muscle relaxing effects. Its common side effects are those of all benzodiazepines and are related to CNS depression; especially drowsiness, incoordination and ataxia. It is often used in combination with doxepin to obtain both rapid and prolonged effects on sleep. It may be helpful for restless legs. *Patients must be cautioned that benzodiazepines can be highly addictive.*	IV
Cyclobenzaprine	10 mg qhs	Tricyclic skeletal muscle relaxant. Do not titrate the dose upwards when used for sleep. For use as a skeletal muscle relaxant, see under "Pain." Common side effects are drowsiness, dry mouth and dizziness. Precautions are similar to other tricyclics. For short-term use, reassess periodically.	IV
L-Tryptophan	500 mg-3 gm qhs	The amino acid precursor of serotonin, which increases it CNS levels. Common side effects include dry mouth and drowsiness. Nausea, anorexia, dizziness and headache have been reported with higher doses. Watch for drug interactions, especially with concomitant MAO inhibitors. Interactive side effects with fluoxetine have been reported.	1V

2. *Pain*

Physical Remedies: A practice of gentle muscle stretching and relaxation techniques is usually helpful. Massage therapy, physiotherapy and chiropractic treatments are beneficial to some patients. Patients should avoid pain exacerbation from excessive pressure on tender points, and from immobilized and strained postures. Acupuncture, EMG biofeedback, local and general heat to relieve muscle spasm and overall tension, gentle stretching, postural ad-

justment and relaxation techniques such as post-isometric relaxation can also be tried. Mobilization and manipulation of joints, adjustments directed towards specific postural abnormalities, spray and stretch if tolerated, and myofascial release techniques directed toward fascial tightness may also be helpful. Ultrasound and electronic muscle and nerve stimulation techniques may be tried by therapists trained in their use, e.g., TENS, but have proven to be of limited benefit in providing long lasting pain relief.

The recent development of Synaptic Electronic Activation Technology (SEA Tech.) (114) may be more effective for longer term pain relief and has also resulted in improved sleep patterns and alleviation of fatigue in preliminary experience. SEA Tech. is contraindicated for pregnancy and pacemakers.

The development of devices that generate pulse magnetic fields is under clinical investigation for the treatment of chronic pain. The magnetic pulser MPG4 (115) and Bio-Resonance therapy (116) have been approved by Health Canada as class II medical devices to improve tissue oxygenation, blood flow and healing, reduce edema as a result of injury and to relieve chronic pain from osteoarthritis and musculoskeletal injuries.

Pharmaceuticals for Pain			
NOTE: "LE" in last column stands for "level of evidence"			
Drug	**Dose**	**Effect/Comments**	**LE**
Acetaminophen	325 mg tablets i-ii q4h prn	Use as baseline analgesic therapy. Weak effect, but low incidence of side effects.	IV
Amitriptyline	5-100 mg Start with lowest dose qhs and gradually increase to effective dose schedule, splitting the dose	Low dose tricyclic antidepressants may be effective for some patients in the short-term. Patients should be warned of typical side effects such as weight gain, dry mouth, and morning grogginess at onset. Watch for daytime sedation and cognitive dysfunction. See previous discussion regarding other side effects and precautions. Benefits are usually seen within 2 to 4 weeks. Reassess frequently for effect/side-effect balance. Note: for FMS the level of evidence is I for this use (117).	IV

Drug	Dose	Effect/Comments	LE
Ibuprofen	200 mg qid prn	A nonsteroidal anti-inflammatory drug (NSAID) analgesic. Watch for GI side-effects, especially GI bleeding, as well as hepatic dysfunction, renal dysfunction, peripheral edema, CNS side effects such as headache, dizziness, drowsiness and evidence of hypersensitivities. Use NSAID precautions to prevent GI side effects.	IV
Gabapentin	Build up to 100 mg bid-300 mg tid (see Appendix 8)	Sometimes helpful for severe pain. Structurally related to the neurotransmitter GABA, but of uncertain mode of action. Described as an anti-epileptic and approved for refractory partial seizures. Effects may also include an increase in energy and reduced anxiety and depression (118, page 144). More common side effects include fatigue, somnolence, dizziness, ataxia, nystagmus, tremor, rhinitis and peripheral edema.	IV
Cyclobenzaprine	Up to 10 mg tid as tolerated	Usually taken at bedtime as it causes sedation. Common side effects include drowsiness, dry mouth and dizziness. Less frequent are tachycardia, weakness, fatigue, dyspepsia, nausea, paresthesias, unpleasant taste, blurred vision, insomnia, convulsions and abnormal liver function. Advise patient of side effects of tricyclics. Also used as a muscle relaxant. See previous note under sleep.	IV
Naproxen	250 mg tid	NSAID analgesic. Side effects as indicated above.	IV
Celecoxib	100 mg bid	NSAID analgesic. Side effects as indicated above.	IV
Ketorolac	Oral–up to 10 mg qid. Parenteral–30-60 mg IM 1-2 times per week	NSAID analgesic. Side effects commonly come from the GI tract and CNS and include dyspepsia, abdominal pain, nausea, constipation, diarrhea, flatulence, peptic ulcers, gastrointestinal bleeding, headache, dizziness, somnolence. Watch for hypersensitivity reactions. Use NSAID precautions. Not recommended for long-term use.	IV

Drug	Dose	Effect/Comments	LE
Baclofen	5-20 mg tid as tolerated (see Appendix 8)	For muscle spasm and pain. Mode of action is uncertain but probably a GABA-B agonist. Listed as a muscle relaxant, antispastic. It also has an effect on central pain and is an anxiolytic and may cause increased alertness (118). Side effects include drowsiness, fatigue, dizziness and weakness, headache, insomnia, hypertension, nausea, constipation, urinary frequency and muscular phyotonia.	IV
Rofecoxib	12.5-25 mg daily	NSAID analgesic. Side effects as indicated above.	IV
Nortriptyline	10-100 mg qhs	A tricyclic antidepressant similar to amitriptyline. Side effects such as dry mouth are generally fewer and less severe.	IV
Doxepin	5-100 mg qhs as tolerated	Effect and side-effect profiles are similar to those for amitriptyline.	IV
Patients with severe pain may need stronger analgesics or narcotics. Their use requires a clear rationale with documentation.			

3. *Fatigue:* Before attempting any treatment for fatigue, start by treating sleep disturbances and pain.

   Physical Remedies: Restorative resting postures from yoga and tai chi, breathing exercises, aromatherapy for patients who are not chemically sensitive, massage therapy and craniosacral therapy.

Pharmaceuticals for Fatigue			
Drug	**Dose**	**Effect/Comments**	**LE**
Methylphenidate	5-10 mg bid	CNS stimulant. Use in a.m. for increased energy and alertness. *Caution–may be habit forming with potential for tolerance and abuse.* Common side effects include insomnia, irritability, nervousness and anorexia. Occasionally there is dizziness, drowsiness, headache, dykinesia, palpitations, tachycardia, nausea, hypersensitivity.	IV

Drug	Dose	Effect/Comments	LE
Modafinil	100 mg qam; can add 100 mg at noon	May stimulate central alpha-1 adrenergic receptors. Use in a.m. for increased energy and alertness. *There is a potential for abuse but lower than that for methylphenidate (PDR).* May cause insomnia, nervousness, headache, nausea, dry mouth and dizziness. It may cause dykinesias in more elderly patients. A retrospective review of medical charts of 25 patients treated with modafinil for fatigue associated with various neurological illnesses suggested it was effective in 21 cases (119).	IV
Cyanocobalamin	Start with 1,000 mcg once per week parenterally, IM or deep SC. Build up to a maximum of 3,000 mcg every 2-3 days	Measure B12 and folate levels before commencing this treatment. Patients can be taught to self-administer injections using the same 1cc insulin syringes used by diabetics. Cyanocobalamin should be stored in a cool, dark place to prevent it from being degraded by light. It is recommended that those who do not respond well take 1 mg of folic acid daily in tablet form. To prevent deficiencies of other B complex vitamins, it is recommended that patients supplement their daily diet with multi-vitamins containing B complex and folic acid which are best taken in the morning due to their occasional excitatory effect. See additional comments below. Note: oral and subliminal B12 are usually ineffective.	V
Amantadine	100 mg bid	Dopaminergic antiparkinson, antiviral agent. Common side effects include nausea, dizziness, insomnia, orthostatic hypotension, depression and confusion. Use with caution as side effects can be severe in ME patients. Watch for evidence of hypersensitivity–skin rashes, peripheral edema, confusion, seizures and hallucinations. Always reduce or withdraw dose gradually to avoid neuroleptic malignant syndrome.	V
Dextroamphetamine	5 mg qam and at noon	Use for increased energy and alertness. *Use with caution–high potential for tolerance and abuse.* Side effects include insomnia, irritability, nervousness, dizziness, dysphoria, dyskinesia, headache, tremor, anorexia, constipation, diarrhea, palpitations and tachycardia.	V

B12/Cyanocobalamin: Based on anecdotal reports of CFS patients improving with B12 injections and research studies demonstrating that persons with normal blood counts who had CFS-like neurological symptoms may benefit from injections of cyanocobalamin (120,121,122), Cheney and Lapp began treating CFS patients with cyanocobalamin parenterally. Fifty to eighty percent of their patients reported some improvement. Most patients had normal serum B12 and folate levels prior to treatment. Measurements of homocysteine and methylmalonate levels taken at the Cheney Clinic showed elevation in approximately one/third of CFS patients suggesting a B12 deficiency may be a contributing factor in the symptomology of this subset of patients. Lapp suggested that this may be due to a reduced ability of B12 to be transported into the cell, as major doses of B12 gives marked improvement of energy level, cognitive ability, and mood, and reduced irritability, numbness and weakness in this subgroup. Improvement is usually seen in six weeks (123). Lapp reports treating thousands of patients with high dose B12 over a ten-year period with no evidence of cyanide toxicity even at 15,000 mcg per week, and no serious adverse effects other than some bruising at injection site. Rarely the urine may have a slight pinkish tint following injection but that appears to be benign. The occasional patient may develop an acne-like rash but it responds quickly to a reduced dosage. B12 injections are contra-indicated for patients with kidney failure. Another theory is that hydroxocobalamin is a nitric oxide scavenger and may address suspected elevated nitric oxide/peroxynitrite (124).

4. *Cognitive Dysfunctions*

   Physical Remedies: Mental exercises, reading within capacity, mindfulness meditation, cognitive retraining such as learning new skills and topics. Some patients may think better lying down or in a semi-reclined posture.

Pharmaceuticals for Cognitive Dysfunctions			
Drug	**Dose**	**Effect/Comments**	**LE**
Methylphenidate	5-10 mg bid	See previous discussion under fatigue for dose, effects, side effects and precautions.	V
Modafinil	Start at 100 mg qam. Can add 100 mg at noon	Used to increase alertness. See previous discussion under fatigue for dose, effects, side effects and precautions.	V

Drug	Dose	Effect/Comments	LE
Detro-amphetamine		Used to increase alertness. See previous discussion under fatigue for dose, effects, side effects and precautions.	V
Nimodipine	Start with 30 mg. Check effect on BP. Gradually increase to 60 mg bid as tolerated	A calcium channel blocker of the dihydropyridine type acting primarily on the cerebral circulation. Improves mental clarity in some but not all patients with ME, but may also have a global effect to increase relaxation, reduce fatigue, decrease tender points, and improve exercise tolerance (118). Common side-effects include hypotension, nausea, headache, bradycardia, skin rash and peripheral edema.	V

5. *Dizziness/Orthostatic Intolerance:* Simple instructions to avoid extension and quick rotation of the neck are often sufficient if dizziness is caused by proprioceptive disturbances in the neck. Instruct the patient to get up slowly while holding on to something, and avoid standing for long periods, especially in warm weather. Pumping legs intermittently and the use of support stockings can be helpful. Avoid large meals and dehydration.

   Neurally mediated hypotension (NMH) and postural orthostatic tachycardia syndrome (POTS) can often initially be alleviated by lowering the head by lying down or bending forward and oral NaCl (up to 10-15 gm daily) with an adequate intake of water. High quality sea salt is best as it contains trace minerals but does not contain additives such as aluminum found in ordinary table salt. This effect is often temporary as the body adapts to the increased load of NaCl.

Pharmaceuticals for Orthostatic Intolerance, NMH and POTS
A combination of therapies is suggested: Two placebo-controlled trials of fludrocortisone (125,126) showed no benefit over placebo. Although the 0.1 mg dose of fludrocortisone that was used in an 8 week trial (125) was insufficient to produce a positive effect, some panel members have found it useful in combination with other therapies. For example, start with increasing salt intake, add either a beta blocker such as atenolol, or an alpha 1 agonist such as midodrine. Consider fludrocortisone if the salt seemed to help for a while but then lost its effectiveness. It is possible to use all three approaches–volume expansion (salt or fludrocortisone), beta blockade (to increase the fill time of the heart), and alpha 1 agonist (to increase venous tone and reduce the orthostatic space that blood drops into while the patient is upright). If these approaches do not work, try paroxetine. *Note: before starting this therapy, NMH or POTS should be confirmed with a tilt-table test.*

Drug	Dose	Effects/Comments	LE
Fludro-cortisone	0.05-0.2 mg daily	Use in combination–see above. Increases sodium and water retention and may inhibit vasodilation. As it is a mineralo-corticosteroid, be very careful to monitor the potassium levels. Use minimal effective dose. Side effects are extensions of its effects–excessive fluid retention, potassium loss and hypertension.	V
Midodrine	Start at 2.5 mg tid, increasing to 5 mg tid if tolerated	It is an alpha-adrenergic agonist. Side effects include supine hypertension, palpitations, headache, bradycardia, pruritus, urinary retention. It can be used in conjunction with fludrocortisone since the mechanism of action differs. Note: level of evidence is II for neurocardiogenic syncope (127).	V
Paroxetine	5-10 mg daily qam, increasing to 20 mg daily	A SSRI antidepressant. See pharmaceuticals for depression for general comments and precautions for SSRIs. More anticholinergic side effects than fluoxetine or sertraline. Commonly reported side effects include nausea, somnolence, sweating, tremor, asthenia, dizziness, dry mouth, insomnia, constipation, diarrhea, anorexia and male sexual dysfunction. Level of evidence is II for refractory vasovagal syncope (128).	V
Pindolol	5 mg bid, increasing to 10 mg tid	A beta blocker used to increase ventricular filling, especially if tachycardia is a problem. Side effects include bronchospasm, bradycardia, aggravation of postural hyptension, insomnia, vivid dreams, fatigue, drowsiness, headache, diarrhea, constipation, nausea. *Observe beta blocker precautions.*	V
Atenolol	25 mg daily, increasing to 100 mg in a single daily dose	A beta blocker. Use to increase ventricular filling, especially if tachycardia is a problem. Use in combination with other therapies. Side effects include aggravation of orthostatic hypotension. Note: this and other beta blockers may be useful to correct POTS/NMH but may not help and may aggravate general symptoms of ME/CFS. Note: Level of evidence is II for unexplained syncope and positive upright tilt table test results (129).	V

Vertigo			
Vertigo accompanied by nystagmus, nausea and/or vomiting and often associated with tinnitus and /or impaired hearing acuity requires an anti-nauseant but there is no good treatment.			
Drug	**Dose**	**Comments**	**LE**
Meclozine	25 mg daily, increasing to 25 mg tid	An antiemetic with antihistaminic and anticholinergic properties. Side effects include drowsiness, dry mouth and fatigue.	V

6. *Irritable Bowel Syndrome (IBS):* Use standard therapy, adjusting diet and using antispasmodics and anti-diarrheal agents judiciously as indicated (level V). Watch for food intolerance and conduct food elimination trials.
7. *Anxiety States:* Supportive counseling can be helpful for some patients.

   Physical Remedies: Massage therapy, taking a relaxing warm bath with a combination of herbs like lemon balm, lavender, or thyme and soothing music. Slow deep breathing helps to stretch the chest muscles and diaphragm and relax the whole body. Walking or swimming helps reduce tension if patient is able to do these without strain.

Pharmaceuticals for Anxiety			
Drug	**Dose**	**Effect/Comments**	**LE**
Clonazepam	0.5 mg daily to 0.5 mg tid	A benzodiazepine. Common side effects are the result of CNS depression including drowsiness, over-sedation, impairment of cognition and psychomotor performance, ataxia, and behavioral disturbances. Also watch for increased secretion in upper respiratory passages, increased salivation, nausea, constipation, diarrhea and rashes. *Cautions for all benzodiazepines: potential for tolerance, dependence and abuse. Regularly reassess need. Always reduce medication very gradually to minimize withdrawal reactions.*	V
Buspirone	5 mg 2-3 times daily to max. of 20 mg daily in divided doses	Azaspirone. This should not be used with MAO inhibitors. It is non-sedating and does not lead to tolerance or dependence. Side effects include dizziness, headaches, nervousness, lightheadedness, nausea, anorexia, sweating.	V

Drug	Dose	Effect/Comments	LE
Alprazolam	0.125 mg bid to max. of 2 mg in divided doses	A benzodiazepine. Similar side effects. Watch for daytime anxiety and insomnia, abnormal involuntary movements, headache, irritability, nausea and diarrhea. Cautions as above.	V
Lorazepam	0.5 mg daily to 1.0 mg bid	A benzodiazepine. Watch for drowsiness, dizziness, weakness, fatigue, ataxia, disorientation, nausea, sleep disturbance, headache, rashes. *Cautions as above.*	V
Diazepam	2-10 mg 3-4 times daily	A benzodiazepine. Common side effects are related to CNS depression including drowsiness and ataxia, fatigue, dizziness, nausea, blurred vision, vertigo, headache, urinary retention, constipation, rashes and hypotension. *Cautions as above.*	V
Oxazepam	10 mg daily to 10-15 mg tid	A shorter acting benzodiazepine. Similar side effects but watch for daytime anxiety and early morning insomnia. *Cautions as above.*	V

8. *Depression:*

   Physical Remedies: Psychotherapy, and adjustment of psychosocial aggravators, massage, bright light therapy. Refer for counseling if depression is severe.

Pharmaceuticals for Depression			
SSRIs	First line choice for treatment of depression. Note: They are not usually effective in treating fatigue and may interfere with sleep. They have a lower frequency of anticholinergic, sedating and cardiovascular side effects than the TCAs but possibly cause more gastrointestinal complaints, sleep impairment and sexual dysfunction.		
Drug	**Dose**	**Effect/Comments**	**LE**
Citalopram	5-40 mg daily qam or pm, max. 40 mg daily	A SSRI antidepressant. The usual SSRI side effects and precautions. Common side effects include faintness, palpitations, increased sweating, nausea, trembling, diarrhea, drowsiness, paresthesias anorexia, sinus congestion, and male sexual dysfunction.	V

Drug	Dose	Effect/Comments	LE
Paroxetine	5-10 mg daily qam, going to 20 mg daily, max. 40 mg daily	A SSRI antidepressant. The usual SSRI side effects and precautions. More anticholinergic side effects than fluoxetine or sertraline. Commonly reported side effects include nausea, somnolence, sweating, tremor, asthenia, dizziness, dry mouth, insomnia, constipation, diarrhea, anorexia and male sexual dysfunction.	V
Fluoxetine	5-20 mg daily, max. 40 mg daily	A SSRI antidepressant. Side effects include headache, nervousness, insomnia, somnolence, anxiety, fatigue, tremor, dizziness, nausea, diarrhea, anorexia, dry mouth, excessive sweating and allergic reactions. Do not use in close temporal proximity with MAO inhibitors or tryptophan. See SSRI general comments. A RCT at 20 mg daily dose found fluoxetine to be ineffective, suggesting that the depressive symptoms of ME/CFS differ from those with major depression (130).	V
Sertraline	25-100 mg with evening meal	A SSRI antidepressant. Usual SSRI side effects and precautions. Common side effects include dry mouth, increased sweating, headache, dizziness, tremor, nausea, diarrhea, constipation, dyspepsia, fatigue, insomnia, male sexual dysfunction, somnolence. There is perhaps a lower risk of drug interactions than with the other SSRIs.	V
Fluvoxamine	5-40 mg	A SSRI antidepressant. The usual SSRI side effects and precautions. Common side effects include nausea, vomiting, dry mouth, constipation, insomnia, agitation, tremor, headache, abdominal pain, somnolence, dizziness, asthenia, anorexia and increased sweating.	V
Other Newer Antidepressants			
Venlafaxine	Start at 18.75 mg daily, max. 112.5 mg daily in 2-3 divided doses	A NSRI. Fewer side effects than for SSRIs. Check for possible increase in diastolic blood pressure. Side effects include dizziness, somnolence, insomnia, asthenia, anorexia, nausea, constipation, dry mouth, dizziness, nervousness. See previous note under fatigue. *Watch for drug interactions and do not use in close temporal proximity with MAO inhibitors.*	V

Drug	Dose	Effect/Comments	LE
Nefazodone	50-200 mg daily in bid doses	A selective 5HT 2 receptor antagonist, also an NSRI. Common side effects include asthenia, malaise, chills, feverishness, POTS, nausea, dry mouth, constipation, diarrhea, somnolence, insomnia dizziness, lightheadedness. *Watch for drug interactions. Do not use in close temporal proximity with MAO inhibitors.* There may be less sexual dysfunctional effects than with SSRIs.	V
Buproprion	Start at 100 mg sustained release once daily, going to 150 mg daily as tolerated	An aminoketone with noradrenergic function. It has no anticholinergic sedating or orthostatic side effects, but may have aversive stimulant-like side effects. Other side effects include headache, agitation, anxiety, insomnia, rashes, dry mouth, nausea, rhinitis. A rare serum sickness-like reaction has been reported. *Do not use in close temporal proximity with MAO inhibitors.*	V
Tricyclic Antidepressants (TCA)	Not first line choices for antidepressant effects because many side effect occur at the dose required for antidepressant effects. *Note: As most ME/CFS patients cannot tolerate a dose high enough to get the antidepressant effect, they are listed as a group.*		
Amitriptylin Doxepin Nortriptyline	5 mg hs to 100 mg daily 5-10 mg hs to 75-100 mg daily 10 mg to 50-100 mg daily as tolerated	A tricyclic antidepressant. Not a first-line antidepressant. Keep dose on low side and increase gradually as tolerated. *Advise patients of possible weight gain.* Watch for antihistaminic side effects (sedation) and anticholinergic side effects (constipation, dry mouth urinary hesitancy and blurred vision). Watch for cardiac toxicity (conduction block, arrhythmias), and aggravation of orthostatic hypotenstion, tachycardia; confusional states, agitation, insomnia, ataxia, nausea, allergic manifestations. *Watch for drug interaction and not use in close temporal proximity with MAO inhibitors.* See note under sleep.	V

Herbal Remedy: St. John's Wort: Dose–900-1800 mg of aqueous-alcoholic extract for mild to moderate depression, with a maintenance dose of 300-600 mg per day. While earlier categorized as a monoamine oxidase inhibitor, this has not been confirmed by more rigorous research, and the mechanism of action remains unknown. Hypericin is being investigated as its active ingredient for depression. There is a low incidence of side effects. Those reported have included restlessness, dizziness, GI irritation and allergic reactions. There is a slight risk of photosensitivity, and it may interact with some pharmaceuticals (antidepressants, digoxin and warfarin) (131). The level of evidence is V for St. John's Wort but it is undergoing phase I and II clinical trials. *St. John's Wort should not be used for marked depression and is not to be taken if patient is using antidepressants.*

9. *Others*

NADH: A randomized controlled study showed oral nicotinamide adenine dinucleotide (NADH) to give an overall beneficial effect in 31% of the patients (132).

Magnesium: A randomized, double-blind, placebo-controlled trial of intramuscular magnesium sulphate for six weeks improved the wellbeing of patients who had low red blood cell magnesium (133).

Simple Symptomatic Relief: Simple, safe, self-researched remedies may be taken as long as they are not harmful or expensive.

Treatment Directed to Probable Pathogenic Mechanisms

There is no one single hypothesis that has been adequately confirmed for the pathogenesis of ME/CFS. Very few remedies show adequately demonstrated effectiveness using double-blinded, randomized, large sample, placebo controlled studies. There are too many treatments following various causal hypotheses being tried to mention them all. However, we have included those with some scientific basis and/or recommendations of experts in the field with clinical experience that justifies their inclusion. They are worth pursuing in individual patients as long as they are safe and their side effects remain acceptable. Their value for groups may be confirmed in the future. In the individual case the results of treatment are certain-a remedy works or it does not, what-

ever the mechanism underlying this effect. Always advise patients of possible side effects.

The following are some of the treatments presently being used that are directed at a proposed underlying cause and some are still undergoing investigation. This should be considered as an overview of treatments.

Immune Dysfunction

a. *Immune Stimulator and Viral Modulator*

Pharmaceuticals for Immune Dysfunction			
Drug	**Dose**	**Effect/Comments**	**LE**
Ampligen	200 mg IV twice a week increasing to 400 mg 2-3 times weekly over an 24 week to six month course	Immune stimulator and viral modulator. Ampligen is available in Canada, in a cost recovery program, for moderate to severely ill patients who have been following other treatments and have RNase L abnormalities. Ampligen is a mismatched ds RNA, which induces the interferon/2-5 synthetase pathway, and controls immune dysregulation, possibly caused by an abnormal RNase L enzyme. It may inhibit viral attachment to cellular receptors and/or inhibit intracellular maturation of the virus (134). Initial studies have shown that a baseline 24-week treatment produces positive results (135), continuing to several years. Significant improvements were in exercise capacity, memory and cognitive ability, activity of daily living and fewer emergency room visits and hospitalizations, as compared to controls (136). Possible side effects–flu-like symptoms, myalgia, headaches at initiation (later abated), lightheadedness and facial flushing. RCTs continue.	II

b. *Some Other Immune Modulators in Phase 1 Trials*

Essential Fatty Acids (EFA): Essential fatty acids have been used for their antiviral effect (137). EFA are required to enable the body to resist viral infections and conversely viral infections interfere with essential fatty acid metabolism (138). They are necessary for prostaglandin synthesis and cellular membrane integrity

and help maintain normal fluidity and flexibility in red cell membranes (137). It is speculated that virus may restrict the infected cells' ability to produce dihomogamma-linolenic acid (DGLA) and arachidonic acid (AA) resulting in reduced activity of interferon and reduced antiviral action of EFA, particularly with enveloped virus. Interferon actions on DGLA and AA are important in eliminating virus (137).

In the first placebo controlled study of EFA deficient post-viral fatigue syndrome patients, sixty three patients were given eight capsules (500 mg per capsule) of Efamol Marine which contains 80% evening primrose oil and 20% marine oil, for three months (139). Of the patients in the study, 84% on active treatment vs. 18% on placebo reported improved or much improved symptoms of fatigue, aches and pains, muscle weakness, lack of concentration, dizziness, vertigo, depression and loss of memory. EFA levels returned to normal in the patients showing improvement but not in those who did not improve (139). In a double-blind, placebo-controlled study of 70 patients with chronic postviral fatigue syndrome, four capsules of Efamol Marine were given morning and evening for fifteen weeks (140). Of those patients, 85% on active treatment vs. 17% on placebo showed improvement of the symptoms. Patients on active treatment also reported fewer episodes of cardiac palpitation and tachycardia (137). It is speculated that virus may restrict the infected cells' ability to produce dihomogamma-linolenic acid (DGLA) and arachidonic (AA). This may result in reduced activity of interferon and reduced antiviral action of EFA, particularly with enveloped virus. Interferon actions on DGLA and AA are important in eliminating virus (137). In a later study by Warren et al. (141), symptoms generally improved but not significantly and there were no significant differences between the treatment and placebo groups. Further investigation is warranted. As L-carnitine is required for the transport of EFA, it may be helpful to add as a supplement when taking EFA.

c. *Antiviral Therapies*

Drug	**Dose**	**Effect/Comments**	**LE**
Valacyclovir	1gm q6h for 6-18 months	For a confirmed herpes infection. A nucleoside with anti-herpes simplex and zoster effect. Side effects were not significantly different from placebo but included nausea and headache. It is presently being investigated by double blinded placebo-controlled randomized trial studies (142).	V

Herbal remedies that are said to have an antiviral effect include oil of wild oregano and olive leaf extract.

d. *Antibiotic Treatments for Mycoplasma and Chlamydia* (143)

A number of antibiotics are being investigated for confirmed infections of mycoplasma or chlamydia. As the rationale and dosage protocols for these treatments are still under investigation, it is premature to recommend this treatment. A brief description is included for your information. The antibiotics being investigated include doxycycline (100 mg bid-tid), clarithromycin (750-100 mg daily on a q12h schedule clarithromycin (750-100 mg daily on a q12h schedule), ciprofloxacin (750 mg bid), and azithromycin (500 mg as a single dose). Generally the trials are for 6 months or until improvement is noted, then multiple courses of 6 weeks on followed by a two-week break. Normal gut flora should be replaced and immune boosters are recommended.

Hypothalamic-Pituitary-Adrenal (HPA) Axis Abnormalities

Pharmaceuticals for HPA Axis Abnormalities			
Drug	**Dose**	**Comments**	**LE**
Fludrocortisone	0.1-0.2 mg daily	Suggested to be used in combination with other therapies. See discussion under NMH and POTS	V
Dehydroepinandrosterone (DHEA)	15-90 mg daily (usually 25-50 mg)	For measured DHEA deficiency. Long term use can cause acne, hair loss, hirsutism, deepening of the voice in women, insulin resistance, decreased HDL, cholesterol and hepatic dysfunction and may increase the risk of prostate and breast cancer. Presently in Canada one needs to apply for special authorization from Health Canada on an individual patient basis for the use of DHEA.	V

Central Nervous System/Autonomic Dysfunction

The CNS function abnormalities result in symptoms of cognitive "fog," nonrestorative sleep, and mood disorders. Symptom driven approaches are described in the previous section. There are a number of therapies to correct symptoms resulting from abnormalities of autonomic function, primarily to correct the extremes of orthostatic intolerance.

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 hypoprofusion 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 solitarus (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 mediofrontal 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 reallocate 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 radioisotopic 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 antishock 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 hypercoaguable, 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 adrenocorticotropic 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 what are immunologically "naive" (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 symtomology,

or whether latent pathogens or antibody response to them have been reactivated 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 hypoprofusion 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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APPENDICES

APPENDIX 1. Glossary of Acronyms

2-5A: 2′,5′-oligoadenylates
AA: arachidonic acid
ABC: ATP binding cassette
ACTH: adrenocorticotropic hormone
ADL: activities of daily living
ATP: adenosine triphosphate
CBT: cognitive behavioural therapy
CD45RA: cluster designation (cell surface marker classification)
CDC: Centers for Disease Control
CFIDS: chronic fatigue and immune dysfunction syndrome
CFS: chronic fatigue syndrome
CMV: cytomegalovirus
CPX: cardiopulmonary exercise
CSA™ Actigraph: computer science and application actigraph
DGLA: dihomogammalinolenic acid
DHEA: dehydroepiandrosterone
EBV: Epstein-Barr virus
EEG: electroencephalogram
EFA: essential fatty acids
EMG: electromyogram
FMS: fibromyalgia syndrome
GABA: gammaaminobutyric acid
GET: graded exercise therapy
HCMV: human cytomegalovirus
HDL: high-density lipoprotein
HHV: human herpes virus
HLA: human leukocyte antigens
HPA: hypothalamic-pituitary-adrenal
IADL: instrumental activities of daily living
IBS: irritable bowel syndrome
IgG: immunoglobulin G
IL6: interleukin 6
kDa: kilodalton
LE: level of evidence
LMW: low molecular weight
MAO: monoamine oxidase
MAST: military antishock trousers
MCS: multiple chemical sensitivities

ME: myalgic encephalomyelitis
ME/CFS: myalgic encephalomyelitis/chronic fatigue syndrome
MMPI: Minnesota Multiphasic Personality Inventory
MPS: myofascial pain syndrome
MRI: magnetic resonance imaging
MS: multiple sclerosis
MUGA: multiple gated acquisition
NADH: reduced form of nicotinamide adenine dinucleotide
NK cell: natural killer cell
NMDA: N-methyl-D-aspartate
NMH: neurally mediated hypotension
NSAID: nonsteroidal anti-inflammatory drug
NSRI: norepinephrine serotonin reuptake inhibitor
OT: occupational therapist
PBMC: peripheral blood mononuclear cells
PDR: physicians desk reference
PET: positron emission tomography
PFC: prefrontal cortex
POTS: postural orthostatic tachycardia syndrome
qEEG: quantitative electroencephalogram
QOL: quality of life
RBC: red blood cell
rCBF: regional cerebral blood flow
RCT: random controlled trial
REM: rapid eye movement
RLI: ribonuclease L inhibitor
RNase L: ribonuclease L
SATET: sub anaerobic threshold exercise test
SEA Tech: synaptic electronic activation technology
SF-36®: medical outcomes study short-form general health survey
SIP: sickness impact profile
SPECT: single-photon emission computed tomography
SSRI: selective serotonin reuptake inhibitor
TENS: transcutaneous electrical nerve stimulation
TMJ: temporomandibular joint
TNF: tumor necrosis factor
UFC: urinary free cortisol
VO_2: peak oxygen consumption levels

APPENDIX 2. ME/CFS Symptom Prevalence and Severity

(These prevalence and severity figures are from *A definition-based analysis of symptoms in a large cohort of patients with chronic fatigue syndrome*, P. De Becker, N. McGregor, and K. De Meirleir. *Journal of Internal Medicine* 2001;250:234-240.) A total of 2,073 consecutive patients with major complaints of prolonged fatigue were assessed. Among them 1,578 met the Fukuda criteria and of those, 951 met the Holmes criteria. The figures indicate the differences in prevalence and severity of symptoms between these patient groups.

SYMPTOM	PREVALENCE (%)		SEVERITY (range 0-3)	
	HOLMES	FUKUDA	HOLMES	FUKUDA
Fatigue	100	100	2.8	2.8
Post-exertional malaise	98.8	97.3	2.8	2.7
Attention deficit	95.9	93.0	2.4	2.2
Sleep disturbance	94.8	91.9	2.5	2.4
Headache	92.0	87.8	2.3	2.1
Myalgia	90.1	87.1	2.4	2.3
Memory disturbance	89.3	85.6	2.2	2.0
Muscle weakness	88.3	84.3	2.3	2.1
Gastrointestinal disturbance	85.6	81.8	2.2	2.0
Sore throat	84.1	74.1	2.1	1.9
Exertional dyspnea	83.5	79.2	2.2	2.0
Recurrent flu-like symptoms	80.9	69.7	2.1	1.7
Difficulty with words	80.4	75.5	1.9	1.7
Personality change	77.2	74.4	1.2	1.1
Cold hands and feet	77.2	72.2	2.0	1.8
Arthralgia	77.1	73.3	2.0	1.9
Photophobia	75.8	70.7	1.8	1.6
Difficulty with calculations	75.1	71.6	1.7	1.6
Light headedness	74.6	69.6	1.7	1.6
Visual acuity	74.2	70.9	1.7	1.6
Dysequilibrium	73.7	69.1	1.5	1.4
Hot flushes	72.6	64.8	1.9	1.7
Numbness/parathesia	69.1	66.4	1.6	1.5
Swollen/tender lymph nodes	67.9	57.7	1.6	1.3
Spatial dysfunction	64.5	59.9	1.4	1.2
Muscle fasciculations	64.1	58.5	1.5	1.4
Alcohol intolerance	63.7	59.5	1.7	1.5
Symptom exacerbation in extremes of temperature	58.7	53.9	1.5	1.4
New sensitivities to food/drugs	54.8	48.5	1.3	1.2
Urinary frequency	53.9	47.9	1.3	1.2
Tinnitus	52.1	48.5	1.0	0.9
Diarrhea	45.6	40.8	1.2	1.1
Rashes	45.3	40.0	1.0	0.9
Altered taste, hearing, or smell	42.4	38.0	0.9	0.8
Persistent cough	39.2	35.2	0.8	0.7
Speech difficulties	36.2	31.8	0.7	0.6

APPENDIX 3. Symptom Severity and Severity Hierarchy Chart

NAME_____ DATE _____

1. Rank your symptoms in order of severity, with 1 being your most severe symptom, in the column to the left.
2. Rate severity of symptoms by putting a check mark in appropriate column to the right of symptoms.

SYMPTOM SEVERITY CHART					
RANK	**SYMPTOM**	**ABSENT (0)**	**MILD (1)**	**MODER-ATE (2)**	**SEVERE (3)**
	Post-exertional fatigue: loss of physical and mental stamina, fatigue made worse by physical exertion				
	Long recovery period from exertion: it takes more than 24 hours to recover to pre-exertion activity level				
	Fatigue: persistent, marked fatigue that substantially reduces activity level				
	Sleep Disturbance: non-restorative sleep, insomnia, hypersomnia				
	Pain: in muscles, joints, headaches				
	Memory disturbance: poor short-term memory				
	Confusion and difficulty concentrating				
	Difficulty retrieving words, or saying the wrong word				
	Gastrointestinal disturbance: diarrhea, IBS				
	Recurrent sore throat				
	Recurrent flu-like symptoms				
	Dizziness upon standing or lightheadedness				
	Change in body temperature, erratic body temperature, cold hand and feet				
	Heat/cold intolerance				
	Hot flushes, sweating episodes				
	Marked weight change				

	Breathless with exertion				
	Tender lymph nodes: especially at sides of neck and under arms				
	Sensitive to light, noise, or odors				
	Muscle weakness				
	New sensitivities to food/medications/ chemicals				
	Total Check Marks in column	× 0	× 1	× 2	× 3
	Column Total				

Total Score _____
Overall symptom severity: _____ **mild,** _____ **moderate,** _____ **severe**
(**Mild–**occurring at rest, **moderate–**symptoms that occur at rest become severe with effort, unable to work, and **severe–**often housebound or bedbound.)
Other Symptoms _____
Aggravators _____
Changes in symptoms _____
How good is your sleep on a scale of 1-5? (5–good restorative sleep, 1–no sleep) ____
How do you feel today on a scale of 1-10? (10–terrific, 1–totally bedridden) _____

APPENDIX 4. Signs and Symptoms

As the neurological, immune and endocrine systems are widely distributed, symptoms are numerous, multiform and of variable intensities. Many of the following symptoms are not present in everyone or at all times and, therefore, cannot be included as part of the criteria for diagnosis.

Circulatory System
____ neurally mediated hypotension (NMH)
____ postural orthostatic tachycardia syndrome
____ delayed orthostatic hypotension
____ light-headedness
____ palpitations
____ fluid retention
____ extreme palor
____ bruising

Digestive System
____ lump in throat
____ nausea
____ heart burn
____ abdominal pain
____ irritable bowel syndrome

Neuroendocrine System
____ loss of thermostatic stability–subnormal body temperature or diurnal fluctuations
____ hot flushes
____ excessive sweating or night sweats
____ feelings of feverishness
____ feelings of cold extremities
____ heat/cold intolerance
____ anorexia or abnormal appetite
____ marked weight change
____ hair loss

Musculoskeletal System
____ myalgia
____ muscle cramps, particularly in legs
____ chest pressure and pain
____ arthralgia
____ TMJ

Nervous System
____ persistent fatigue
____ lack of endurance
____ migraines or new onset headaches
____ seizure like phenomena

Sensory
____ hypersensitivity to pain
____ hyper-responsiveness to noxious stimuli
____ perceptual & dimensional distortions
____ feeling of burning or swelling
____ overload phenomena
____ loss of cognitive map
____ altered taste and/or smell

Cognitive
____ difficulties processing information
____ concentration problems
____ confusion
____ difficulties with word retrieval
____ word mix-ups
____ short-term memory difficulties
____ slowness in cognitive processes

Motor and Balance
____ muscle weakness or paralysis
____ poor balance, ataxia & tandem gait
____ clumsiness & tendency to drop things
____ difficulty in tandem gait
____ atypical numbness or tingling

Sleep Disturbances
____ sleep disturbance–hyper- or insomnia
____ non-refreshing sleep

Visual and Auditory Disturbances
____ photophobia
____ visual changes or eye pain
____ double, blurred or wavy vision
____ dry or itchy eyes
____ tinnitus–buzzing or ringing in ears
____ hyperacusis & cocktail party phenomena

Neuropsychological
____ loss of adaptability
____ worsening of symptoms with stress
____ emotional flattening or personality change
____ anxiety &/or panic attacks
____ reactive depression

Immune System
____ tender lymph nodes
____ recurrent sore throat
____ recurrent flu-like symptoms
____ new sensitivities to medications, chemicals

Reproductive System
____ dysmenorrhea
____ PMS or irregular menstrual cycles
____ loss of sexual libido or impotence

Respiratory System
____ exertional dyspnea
____ sinusitis
____ persistent cough & wheezing

Urinary System
____ urinary frequency, bladder dysfunction

APPENDIX 5. ME/CFS Clinical Diagnstic Worksheet

NAME	**DATE**

☐ 1. **Fatigue:** 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 Fatigue:** There is an inappropriate loss of physical and mental stamina, rapid muscular and cognitive fatigability, post-exertional fatigue and/or malaise and/or pain and a tendency for other associated symptoms within the patient's cluster to worsen. There is a pathological slow recovery period–usually 24 hours or longer.

☐ 3. **Sleep Dysfunction:*** There is unrefreshed sleep or sleep quantity or rhythm disturbance such as reversed or chaotic diurnal sleep rhythm.

☐ 4. **Pain:*** There is a significant degree of myalgia. Pain can be experienced in the muscles and joints and is often 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 inability to focus vision. Ataxia, muscle weakness and fasciculations are common. There may be overload phenomena: cognitive, sensory–e.g., photophobia and hypersensitivity to noise–and/or emotional overload, which may lead to "crash"[1] periods and/or anxiety.

☐ 6. **At Least One Symptom from Two of the Following Categories:**

____ **Autonomic Manifestations:** orthostatic intolerance–NMH, POTS, delayed postural hypotension, vertigo; light-headedness, extreme pallor; nausea and IBS; urinary frequency and bladder dysfunction; palpitations with or without cardiac arrhythmia; palpitations, and exertional dyspnea.

____ **Neuroendocrine Manifestations:** loss of thermostatic stability–subnormal body temperature and/or marked diurnal fluctuation, sweating episodes, recurrent feeling of feverishness and cold extremities; intolerance to heat and cold; marked weight change–anorexia or abnormal appetite; loss of adaptability and tolerance for stress, worsening of symptoms with stress and a slow recovery.

____ **Immune Manifestations:** tender lymph nodes, recurrent sore throat and 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.

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

To be included, the symptoms must have begun or have been significantly altered after the onset of the 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 are often unique to a particular patient. The manifestations fluctuate and may 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 no sleep dysfunction but no other diagnosis fits except ME/CFS. A diagnosis of ME/CFS should only 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: Confirm 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, iron overload syndrome, other treatable forms of anemia, diabetes mellitus, 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, polymyosistis, and polymyalgia rheumatica; immune disorders such as AIDS; neurological disorders such as 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/or imaging. If a potentially confounding medical condition is under control, then the diagnosis of ME/CFS can be entertained if the patient meets the criteria otherwise.

Co-Morbid Entities: Fibromyalgia syndrome, myofascial pain syndrome, temporomandibular joint syndrome, irritable bowel syndrome, interstitial cystitis, irritable bladder syndrome, Raynaud's phenomenon, prolapsed mitral valve, migraine, allergies, multiple chemical sensitivities, thyroiditis, sicca syndrome, depression, Hashimoto's, 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 but has insufficient symptoms to meet the criteria for ME/CFS, it should be classified as idiopathic chronic fatigue.

_____ **Patient meets the criteria for ME/CFS**
_____ **Patient meets the criteria for Idiopathic Chronic Fatigue**

NOTES: _____

APPENDIX 6. American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia

1. **History of widespread pain.** Pain is considered widespread when all of the following are present:
   - in both sides of the body, above and below the waist (including low back pain)
   - axial skeletal pain (cervical spine, anterior chest, thoracic spine or low back)
   - widespread pain must be present for at least 3 months
2. **Pain in at least 11 of 18 tender point sites on 4 kg palpation.** (Approximately 4 kg force–thumbnail whitens.)
   - **Occipital (2)**–bilaterial, at the suboccipital muscle insertions
   - **Low Cervical (2)**–bilateral, at the anterior aspects of the intertransverse spaces at C5-C7
   - **Trapezius (2)**–bilateral, at the midpoint of upper border
   - **Supraspinatus (2)**–bilateral, at origins, above the scapula spine near the medial border
   - **Second rib (2)**–bilateral, upper lateral to the second costochondral junctions, just lateral to the junction on the upper surface
   - **Lateral epicondyles (2)**–bilateral, 2 cm distal to the epicondyles in the brachioradialis muscle
   - **Gluteal (2)**–bilateral, in upper outer quadrants of buttocks in anterior fold of muscle
   - **Greater trochanter (2)**–bilateral, posterior to the trochanteric prominence
   - **Knee (2)**–bilateral, at the medial fat pad proximal to joint line

For a tender point to be considered "positive" the palpitation must be painful. "Tender" is not to be considered "painful."

(This contains slight changes in wording but not in content.)

The American College of Rheumatology 1990 Criteria for the Classification of Fibromyalgia: Report of the Multicenter Criteria Committee. Wolfe, F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, Tugwell P, Campbell SM, Abeles M, Clark P, Fam AG, Farber SJ, Fiechtner JJ, Franklin CM, Gatter RA, Hamaty D, Lessard J, Lichtbroun AS, Masi AT, McCain GA, Reynolds WJ, Romano TJ, Russell IJ, Sharon RP. ©Arthritis and Rheumatism, 1990 Februrary, Vol. 33, No. 2, pages 160-172. Reprinted by permission of Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc.

APPENDIX 7. ME/CFS Patient Evaluation Worksheet

NAME_____ DATE _____

A. 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.

1. FOCUS ON THE PRINCIPAL SYMPTOMS OF ME/CFS: Including post-exertional malaise, fatigue, sleep dysfunction, pain and symptoms from neurological/cognitive, autonomic, endocrine and immune dysfunctions. Examine the course of the symptoms, with special attention to the worsening of symptoms after exertion, prolonged recovery and fluctuating course.

2. PRESENTING COMPLAINT AND AGGRAVATING/AMELIORATING EVENTS

Date of onset _____ **Trigger or prodromal event** _____

Symptoms at onset _____

Progression of symptoms _____

Duration of symptoms_____

Hierarchy of quality and severity of current symptoms (Appendix 2) _____

Worsening of symptoms with exertion: symptoms which require prolonged recovery

Secondary symptoms & aggravator _____

Energy/Fatigue (great 100%): good day _____%, bad day _____%
Sleep Quality _____
Pain Severity: absent _____, mild _____, moderate _____, severe _____
Quantify severity of total burden of symptoms and current level of physical function

3. MEDICATION HISTORY: Current, past, prescribed and other therapies, sensitivities to medications _____

4. **SENSITIVITIES AND ALLERY HISTORY:** Including new sensitivities and allergies and change in status of pre-existing ones _____
_____

5. **PAST HISTORY:** Earlier illnesses, exposure to environmental, occupational and residential toxins _____
_____
_____
_____

6. **FAMILY HISTORY:** _____
_____
_____

7. **SYSTEMS REVIEW:** Many symptoms involve more than one system. Attention should be paid to:
MUSCULOSKELETAL: Myalgia, muscle weakness, or arthralgia _____
_____
_____

CNS: Fatigue with post-exertional exacerbation, neurocognitive complaints, headaches, sleep disturbance_____
_____
_____

ANS & CARDIORESPIRATORY: Palpitations, exertional dyspnea, symptoms suggestive of neurally mediated hypotension (NMH), postural orthostatic tachycardia syndrome (POTS), delayed postural orthostatic intolerance, vertigo, light-headedness, respiratory disturbances, extreme pallor _____
_____
_____
_____

ANS & GI & GU: Intestinal or bladder disturbances with or without IBS _____
_____
_____

NEUROENDOCRINE: loss of thermostatic stability, heat/cold intolerance, marked weight change, loss of adaptability and tolerance for stress and slow recovery, emotional lability_____
_____
_____
_____

IMMUNE: General malaise, 'flu-like' feeling, recurrent sore throat, hypersensitivity to foods, medications or chemicals _____
_____
_____
_____

B. **PHYSICAL EXAMINATION:** Standard physical exam, with **attention paid to: MUSCULOSKELETAL SYSTEM:** including FMS tender point exam (Appendix 6). Check joints for inflammation. Document Muscle strength._____
Positive tender points _____/18. Meets criteria for FMS _____
_____
_____
_____

CNS: Including reflex examination *(Reflex examination during neck flexion and extension may accentuate abnormalities arising from cervical myelopathic changes)*_____
_____
_____

APPENDIX 7 (continued)

Tandem walk: forwards _____ backwards _____

Romberg test _____

- **COGNITIVE:** Ability of patient to remember questions, cognitive fatiguing (e.g., serial 7 subtraction) and cognitive interference (e.g., serial 7 subtraction and tandems done simultaneously) _____

CARDIORESPIRATORY SYSTEM: Arrhythmias _____

BP (first lying down) _____/_____ **BP** (immediately after standing) _____/_____

GI SYSTEM: Increased bowel sounds, abdominal bloating and tenderness_____

ENDOCRINE SYSTEM: Thyroid, adrenal and pituitary dysfunction _____

IMMUNE SYSTEM: Tender lymphadenopathy in the cervical, axillary inguinal regions (especially in acute stage) _____

Crimson crescents in the tonsillar fassae _____

C. LABORATORY AND INVESTIGATIVE PROTOCOL: A thorough work up must be done.

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, risk factors & co-morbid conditions.

FURTHER LABORATORY TESTS: Diurnal cortisol levels, 24 hour urine free cortisol; hormones including free testosterone, B12 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, chest x-ray, TB skin test and HIV. Do testing for 37-kDa 2-5A RNase L immunoassay when it becomes available_____

DIFFERENTIAL BRAIN FUNCTION & STATIC TESTING: For those with positive neurological findings

X-RAY &/or MRI of brain and spinal cord: To rule out multiple sclerosis (MS) and other primary neurological disorders. ***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***_____

_____

TILT TABLE TEST: (If indicated, it should be done prior to giving medication for orthostatic intolerance) _____

_____

SLEEP STUDY: To show decrease in time spent in stage 4 sleep or rule out treatable sleep dysfunctions _____

_____

qEEG, SPECT and PET Scans and Spectography: _____

_____

24-HOUR HOLTER MONITORING: Repetitively oscillating T-wave inversions and/or T-wave flats during 24-hour monitoring. Note: this pattern may not be reported or subsumed under non-specific T-wave changes _____

_____

_____ **ME/CFS: If the patient's presentation meets the criteria for ME/CFS, classify the diagnosis as ME/CFS, except when the specified exclusions are present**

_____ **Idiopathic chronic fatigue: Chronic fatigue but does not meet the criteria for ME/CFS**

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

APPENDIX 8. Protocol for Therapeutic Medication Trials

Prior to and during the trial, keep other therapies and activities as constant or regular as possible. Keep a symptom diary for two weeks prior to testing and thereafter during trials, marking down good effects, bad effects and side effects. Try to include a standardized session of reading or cognitive activity and physical exercise within fatigue limits on a daily basis and mark down the results.

There should be a two-week washout between trials.

If it is important to distinguish specific from nonspecific effects for research or other reasons**, and with the patient's permission**, placebo periods can be interspersed.

Example 1. GABAPENTIN: 100-300 mg tid (118)
Start 100 mg capsule daily q AM × 3 days
100 mg bid × 4 days
100 mg tid × 7 days
REASSESS for decision to discontinue, lower dose, stay at above dose, or increase dose in stages to maximum recommended.

Example 2 BACLOFEN: 10-20 mg tid (118)
Use a 10 mg tablet
Start 1/2 tablet daily q AM × 3 days
then 1/2 tablet bid × 4 days
then 1/2 tablet tid × 7 days
then 1 tablet q AM, 1/2 tablet at noon and hs × 3 days
then 1 tablet q AM and noon and 1/2 tablet hs × 3 days
then 1 tablet tid × 7 days
REASSESS for decision to discontinue, lower dose, stay at above dose, or increase dose in stages to maximum recommended.

APPENDIX 9. Poor Balance, NMH, POTS and Vertigo

Many patients with ME/CFS have poor balance and some suffer from NMH, POTS, delayed postural orthostatic intolerance and occasionally vertigo.

A. Guidelines for Patients for "Finding Center" for Balance–Jones & Clark (102)

1. Stand with your feet shoulder width apart, both heels flat on the floor
2. Gently rock forward until you get a sensation of becoming "heavier" and a bit off balance.
3. Gently rock back, feel the point where you seem lighter and in balance. As you continue backward, you will notice that you become heavier and unbalanced. Now rock forward to the point where you feel balanced. This is your center.
   Try keeping your posture such that you stay in the centered position.

B. The Cawthorne/Cooksey System (98,99)

If either or both of the balance centers of the ears are damaged or send unequal impulses to the brain, your equilibrium is upset and you may dizzy and/or loose your balance. Although this can be frightening, the following exercises can help reduce your dizziness and improve your balance.

Start at stage 1 and do the first exercise for at least five minutes three times a day. When this exercise no longer makes you dizzy, move on to the next exercise. By doing the exercises with your eyes closed, it helps your eyes and muscles have a better sense of balance. It is important to relax during all the exercises. When you feel comfortable doing one exercise, you can move on to the next. Do not rush through the exercises or worry about how long you stay at one level. It may take a number of months to progress through these exercises. Gradually introduce movements until you begin to feel dizzy as the more often dizziness is induced, the more quickly the brain's adjusts for it. If you think that an exercise may make you dizzy, have someone stand beside you in case you loose your balance. Medications may also be required

Stage 1: Head kept still–in bed or sitting

1. Look up and down and from side to side.
2. Focus on your finger at arm's length and then follow the finger as you move it to one foot in front of your eyes.

Stage 2: Head and eye movements while sitting

1. Bend your head forwards and backwards and then from side to side slowly at first and then faster with eyes open.
2. Repeat the whole exercise with your eyes closed.

Stage 3: Head and body movements while sitting

1. Practice shoulder shrugging and circling.
2. Pick up an object off the ground and lift it up without taking your eyes off it.
3. Practice passing an object (such as a ball or bean bag) from hand to hand under the knees.

Stage 4: Standing exercises

1. Try standing without support–first with eyes open and then with eyes closed.
2. Try turning around while standing.
3. Throw a large ball from hand to hand while standing.

Stage 5: Moving about

1. Walk across the room and around a chair with your eyes open and then with your eyes closed.
2. Circle around a person while throwing a large ball back and forth between you.
3. Stand back to back with somebody. Pass a large ball between your legs and receive the ball back from him above the head. Try this as quickly as possible.
4. Walk up and down a slope with eyes open and then closed.
5. Walk up and down steps with eyes open and then closed. Be sure to hold on to a hand-rail.
6. Play games involving stooping and stretching.

APPENDIX 10. Karnofsky Performance Scale (234)

Able to carry on normal activity; No special care is required.	**100**	Normal; no complaints; no evidence of disease
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work, able to live at home and care for most personal needs; a varying amount of assistance is needed.	**70**	Cares for self, unable to carry on normal activity or to do active work.
	60	Requires occasional assistance but is able to care for most needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	**40**	Disabled: requires special care and assistance.
	30	Severely disabled; hospitalization is indicated although death is not imminent.
	20	Very sick; hospitalization necessary; active supportive treatment is necessary.
	10	Moribund; fatal processes progressing.
	0	Dead

APPENDIX 11. Work Place Aggravators

When assessing a patient's ability to work, it may be helpful to consider the following common occupational or work place aggravators. The following list has been adapted from the description of work place aggravators for fibromyalgia syndrome by Waylonis GW et al. (235):

- Prolonged sitting
- Prolonged writing
- Prolonged desk work
- Prolonged telephone use
- Prolonged bending over work surface
- Prolonged standing and walking
- Prolonged driving
- Unsupported extension of arms
- Repeated moving and lifting
- Heavy lifting or bending
- House cleaning
- Computer work
- Multi-tasking
- Fast paced and/or complex work environment
- Sensory overload–light, sound, odors, motion and confusion
- Change in work hours–e.g., shift work
- Environmental factors–e.g., cold, pollutants, chemicals
- Stress

APPENDIX 12. Tests That May Be Used Inappropriately in the Assessment of ME/CFS

The tests commonly being used to assess the physical capabilities and sincerity of effort of ME patients are often interpreted inappropriately, as they do not consider the severity and fluctuation of symptoms or the activity level over an extended time frame. **Functional Capacity Evaluations (FCE)** may not reflect the severity and complexity of the illness, nor do they usually assess cognitive fatigue and dysfunction. They are usually one-stop assessments and lack reliable methods for determining subject participation (sincerity of effort) (236). When a patient is unable to perform at normal levels, he/she is often regarded as being insincere or a malingerer; however the reliability standards are set on healthy individuals. The performance in the limited, uncharacteristic and artificial situation of a FCE does not indicate the patient's endurance for a full workday schedule in her/his natural work environment which may be full of noise distractions and interruptions (88). FCEs do not reflect the widespread symptoms, and their fluctuation in intensity and interactions that are seen in the actual illness. For example, one often does not see the full extent of muscle and cognitive fatigue reaction to physical or mental exertion until a day or two following testing, or the fatigue that may be cumulatively increased by activities continued over longer stretches of time.

The **MMPI** was designed to assess the personality features of normal and psychiatrically ill people. It is seldom useful for patients with ME/CFS. This and similar tests do not consider that symptoms such as fatigue, poor sleep, headaches, dizziness, feeling weak, etc., may be due to biological disorders (237). Without taking organically caused physical symptoms into account, the interpretation can be misleading and erroneous.

Monitoring a Hypothetical Channelopathy in Chronic Fatigue Syndrome: Preliminary Observations

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ABSTRACT. This study was aimed at monitoring of a previously suggested channelopathy in Chronic Fatigue Syndrome, and at searching for possible explanations by means of immune system characteristics. Twenty-seven CFS patients and 20 age and sex matched healthy volun-

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teers were recruited. RNase L-ratio, percent of the norm of whole body potassium content, serum electrolytes (sodium, calcium and potassium), immune cells, blood cell count and erythrocyte sedimentation rate were determined. More than fifty percent of our patients presented with abnormal whole body potassium content. Eight patients had increased, while six had depleted potassium content. Discriminant function analysis revealed that the CFS patients and control subjects could be differentiated on immunophenotyping with the predominant cell differences being the increase in CD19+ CD5+ (mature B-) cells and the decrease in CD3− CD16+ CD56+ (NK) cells in both the percentage and count distributions. The fall in NK-cells was very strongly associated with increases in the RNase L-ratio and falls in serum calcium levels. In addition, four patients with low serum calcium levels showed lower whole body potassium levels. In conclusion, these observations suggest a channelopathy in a subset of CFS patients, probably induced by the deregulated 2-5A RNase L antiviral pathway.

KEYWORDS. Chronic fatigue syndrome, channelopathy, immunity, RNase L, potassium

INTRODUCTION

Chronic Fatigue Syndrome is characterized by numerous symptoms, but there does not appear to be a single underlying cause for all patients. Indeed, Holmes (1988) (1) and Fukuda (1994) (2) CDC-criteria gave rise to a heterogeneous patient-group. This heterogeneity therefore requires the investigators to delineate those features that may be causative as compared to those features that may result from secondary host responses or co-morbid disease.

There is a growing international consensus to differentiating Chronic Fatigue Syndrome into clinically relevant subcategories that may represent either different disease states or to differentiate the potential co-morbid illnesses. Therefore, assessment of the deregulation of the 2-5A synthetase/RNase L antiviral pathway (3) and its associations with biochemical, immune and symptom changes is of prime importance. A recent report (4) suggests possible associations between the deregulated pathway and a channelopathy (5,6,7) in chronic fatigue syndrome. Thus

an assessment of the associations between the RNase L-ratio and electrolyte changes may allow determination of any association between RNase L-anomaly and a potential channelopathy as assessed by a serum electrolyte panel and whole body potassium determination. We present here a study of a small sample of CFS patients (and matched healthy controls) in which we use uni- and multivariate analyses to assess any possible associations between the RNase L-ratio, electrolytes, biochemical and immunological parameters.

METHODS

Study Setting and Sample

The study was conducted in Brussels, at a university-based outpatient clinic (Vrije Universiteit Brussel), and approved by the University hospital ethics committee. We enrolled twenty-seven consecutive patients, seeking care for prolonged fatigue as their major complaint who complied with the Fukuda (2) definition. Patients were also evaluated for eligibility according to the Holmes case definition (1) although this was not used as exclusion-criteria. Twenty age and sex matched healthy volunteers were recruited among college students and hospital employees. Immune cells were counted in the blood samples of the control subjects, RNase L-ratio, erythrocyte sedimentation rate, serum electrolytes and whole body potassium content were determined. Before blood collection, they were questioned about medication-use or illness during the past three months.

The selection and characterisation of the subjects involved several steps. All subjects underwent an extensive medical evaluation, consisting of a standard physical examination and medical history, an exercise capacity test, a symptom checklist and routine laboratory tests. The laboratory tests included a complete blood cell count, determination of the erythrocyte sedimentation rate, a serum electrolyte panel, measures of renal, hepatic, and thyroid function, and rheumatological and virological screenings. In a number of cases further neurological, gynaecological, endocrinological, cardiac, psychiatric and/or gastro-intestinal evaluation was performed. When positive results were found in any of the evaluations that met the Fukuda (2) exclusionary criteria, the patients were not included in this study. The medical records were reviewed to determine if patients suffered from organic or psychiatric illnesses that could explain their symptoms. All patients completed a questionnaire

which included demographic information, dates of onset and current health status. Afterwards the subjects were examined by one physician (KDM), who interviewed the patients with respect to their signs and symptoms. Subjects were excluded if they were < 18 or ≥ 66 years of age, using one of the medications listed in Table 1, or reported an episode of diarrhoea or vomiting. All patients and controls were Caucasian. Demographic characteristics of the sample are presented in Table 2.

Measurement of Whole Body Potassium by Gamma-Ray Spectrometry

Whole body potassium was measured by gamma-ray spectrometry, which assesses isotope ^{40}K. A naturally occurring gamma-radiation-emitting isotope, ^{40}K exists in the human body at a constant 0.012% of total body potassium (8,9,10). Gamma-ray spectrometry occurred at the isotope-centre of Brugmann hospital (AZ-V.U.B. & U.L.B.), using a whole body scintillation counter (model 8102A, Nuclear Enterprises, Brussels), consisting out of four detectors (voltage sensitive preamp-

TABLE 1. List of Medications Used for Exclusion

Diuretica
Angiotensine-converting enzyme inhibitor
Potassium supplements
Therapeutic steroids*
Antibiotics*

* glucocorticoids and some forms of antibiotics stimulate secretion of renal potassium, which in turn causes hypokalaemia

TABLE 2. Demographic Features of Our Sample

	Patients	Controls	*P*-value
N	27	20	
# fulfilling Holmes et al.	16	0	
# fulfilling Fukuda et al.	27	0	
# males (%)	2 (7.4)	2 (10)	.759
# females (%)	25 (92.6)	18 (90)	
Mean age	41.1	38.6	.371
SD age	8.6	10.4	

lifier, model NE 5288B). The same equipment was used in the study of Burnet et al. (7). The counter consists out of four detectors (voltage sensitive preamplifier, model). The detectors were enclosed within a lead lined pre-1945 shield of wall thickness approximately 15 cm, to reduce background radiation to a minimum and to increase sensitivity. Subjects were dressed in clean hospital gowns, and laid supine for 30 minutes on a transparent perspex sheet. The latter enables the operator to accurately align the lower detectors with a selected axis or area of the patient. Data acquisition is performed by an AccuSpec NaI Plus board computer interface (Canberra Industries). Calibration was performed using known concentrations of isotope in water phantoms (plastic bottles). Phantom counts showed a coefficient of variation (CV) of 1.1% and background CV counts of 2.3%. Total body potassium results are expressed in mEq/kg, and also as a percentage of expected normal value. Expected normal values are predicted on the basis of height, weight, age and sex from a database of 61 healthy subjects, previously measured using the same whole body counter (12).

RNase L-Ratio Determination

Within four hours of phlebotomy, peripheral blood mononuclear cell extracts (PBMC) were separated from heparinized blood (30 ml) by Ficoll-Hypaque density gradient centrifugation. In addition, PBMCs were stored at −70°C until cytoplasmic extraction preparation (3). The latter was performed in the presence of protease inhibitors aprotinin, leupeptin, pefabloc-SC and EDTA (Roche Biochemicals, Mannheim, Germany). Standard laboratory procedures were used to separate serum from coagulated blood, and to store it at −70°C until analysis. A modified Bradford assay method (Bio-Rad Laboratories, Hercules, CA) was used for quantification of total proteins in the patients' cell extracts and serum. Briefly, 200 μg of PBMC extract was incubated with a metaperiodate (10 mM final concentration, pH 4.75) oxidized 2-5A trimer radiolabeled at the 3′ end with 32P-pCp as the receptor ligand, at 2-4°C for 15 minutes. In addition, it was covalently attached to the binding proteins by the addition of cyanoborohydride (20 mM in 100 mM phosphate buffer, pH 8.0). This reduction reaction was allowed to progress for 20 minutes at 2-4°C. Sodium dodecylsulfate polyacrylamide gel electrophoresis (SDS-PAGE) buffer and a tracking dye were added to the samples, and incubated at 95°C for 5 minutes followed by separation using standard SDS-PAGE with a 4% stacking and a 10% separating gel. The gel was dried and autoradiography was performed (Bio-Rad

Laboratories Molecular Imager® Fx, Hercules, CA). Densitometric analyses of the autoradiographs was followed by quantification of any present 2-5A-BP (using specialized software: Quantity One® Software, Bio-Rad Laboratories, Hercules, CA). RNase L-ratio was counted using following equation: RNase L-ratio = [low molecular weight RNase L]/[high molecular weight RNase L] $\times$ 10.

Immunophenotyping

Anticoagulated blood (EDTA) was collected between 9 and 11 a.m. and used for white blood cell enumeration, differential counts (Celldyn 4000, Abbott Laboratories, Abbott Park, IL 60064, USA) and flow cytometric studies. Lymphocyte populations were analysed with dual colour direct immunofluorescence on a EPCS® XL flow cytometer (Carlter, Miami, FL, USA), with aid of the "System I™" computer software. One hundred µl of whole blood was incubated with the appropriate combination of monoclonal antibodies for 25 minutes at 4°C. Then red cells were lysed using lysis buffer (Becton Dickinson) for 7 minutes, spun down and washed once with 2 ml phosphate buffered saline (PBS). Resuspension was immediately followed by cell analysis. Commercially available (Becton-Dickinson) phycoerythrin (PE) or fluorescein isothiocyanate (FITC) monoclonal antibodies were used and are listed in Table 3. Estimates of absolute numbers of lymphocyte subsets were determined by multiplying peripheral lymphocyte counts by the percentage of each surface marker.

Statistical Analysis

All the data were administered into Excel 98.0. The data were coded and transferred to the University of Newcastle, Callaghan, Australia where the statistical analysis was done. Data distributions were evaluated for normality and linearity and those data not showing normality were transformed for multivariate analysis. Subject characteristics were assessed using chi-square probability and student t-tests. Uni-variant group differences were assessed on un-transformed data using the student t-test. Immunophenotyping profiles were assessed by forward stepwise discriminant function analysis as both percentage distribution and cell counts. The patient classification capacity of the discriminant function module was used to assess the patient compliance within each model. This allowed an evaluation of the predictive capacity of the different immunophenotypes in determining a potential diagnosis of CFS.

TABLE 3. Monoclonal Antibodies Used for Immunophenotyping

Complementarity Determination	Monoclonal Antibodies	Subset
CD2+	Leu5b+FITC	E-rosette receptor
CD3+	Leu4+FITC	T-cells
CD3+HLADR+	Leu4+HLADR+PE	Activated T-cells
CD25+	IL2R1-PE	Activated cells
CD4+	Leu3a+FITC	Helper/inducer T-cells
CD4+CD45RA−	Leu3aLeu18-PE	Memory CD4-cells
CD4+CD45RA+	Leu3aLeu18+	Virgin CD4-cells
CD8+	Leu2a+FITC	Cytotoxic/Suppressor T-cells
CD8+CD11b+	Leu2aLeu15+PE	Suppressor cells/NK-subset
CD8+CD11b−	Leu2aLeu15-	Cytotoxic T-cells
CD19+	Leu12+PE	B-cells
CD19+CD5+	Leu1+Leu12+	Mature B-cells
CD3− CD16+CD56+	Leu4-Leu16+PE Leu19+PE	NK-cells
CD3+CD16+CD56+	Leu4+Leu16+Leu19+	Subset cytotoxic T-cells

These data were processed using Access97™ (Microsoft, Redmond, WA, USA), Excel97™ (Microsoft) and Statistica™ (Ver. 5.1, Statsoft, Tulsa, OK, USA).

RESULTS

Twenty-seven CFS patients were recruited who complied with the Fukuda criteria. Of the 27 Fukuda defined CFS patients, 16 patients (59.3%) also fulfilling the Holmes criteria. No difference in age or sex distribution was found between patients and healthy volunteers (C = controls) (mean age ± SD: CFS = 41.1 ± 8.6, C = 38.6 ± 10.4 years; age range: CFS = 19-66, C = 21-58 years; N and percent (%) females: CFS = 25 or 92.6%, C = 18 or 90%).

Table 4 shows the standard biochemical measures, ranges and prevalence of subjects outside the reference ranges. Six patients had elevated c-reactive protein (CRP) levels and 10 elevated erythrocyte sedimentation rates (ESR). The patients with an elevated c-reactive protein levels were more likely to have a raised ESR (raised CRP = 5 of 6; normal CRP 5 of 21–$P < 0.008$) consistent with an acute phase reaction. Patients with raised CRP levels had higher serum calcium levels than the remaining CFS patients (CRP > 4 = 9.2 ± 0.4; CRP < 4 = 8.9 ± 0.2–$P <$

TABLE 4. Standard Measures and Prevalence Outside Reference Ranges for the CFS Patients

Parameter	Mean (95%CL)	Prevalence N (%)	Reference Range
RNase-L	19.8 (10.1-29.6)	23 (85.2) High	< 2.0 LMW/HMW × 10
Neutrophil count	4.0 (3.4-4.6)	0	1.48 − 7.10 × 103/mm^3
Lymphocyte count	2.3 (1.9-2.7)	0	0.68 − 4.22 × 10^3/mm^3
C-reactive protein	3.4 (2.0-4.8)	6 (22.2) High	< 4 mg/L
Erythrocyte sedimentation rate	10.7 (7.0-14.3)	10 (37.0) High	0-10 mm/h
Serum sodium	142 (141-142)	0	137-145 mEq/L
Serum calcium	8.9 (8.8-9.1)	4 (14.8) Low	8.6-9.8 mg/dL
Serum potassium	3.8 (3.8-3.9)	0	3.6-5.0 mEq/L
Whole body potassium	37.4 (34.4-40.4)		
% Whole body potassium	103 (97-109)	6 (22.2) Low 8 (29.6) High	90%-110%
Non-serum K^+	33.5 (30.5-36.5)		
Serum K^+: Non-serum K^+	8.7 (8.0-9.4)		

% whole body potassium = % of the norm (expected normal values, in accordance to subjects' age, sex, weight and height); LMW = low molecular weight; HMW= high molecular weight.

0.05). Patients with raised ESR levels had lower serum potassium levels than the remaining CFS patients (ESR >10 = 3.7 ± 0.1; ESR < 10 = 3.9 ± 0.2–$P < 0.02$). Four patients had low serum calcium levels and these four CFS patients also had lower whole body potassium levels (low Ca = 31.4 ± 4.3; normal Ca = 38.4 ± 7.7–$P < 0.05$). Thus CFS patients do have an alteration in electrolyte levels which appear partially associated with alterations in measures of acute phase reactions.

Table 5 shows the uni- and multivariate analyses of the differences in immunophenotypes between the CFS and control groups. The CFS patients had increases in the B-cell (CD19+), the activated T-cell (CD25+) and mature B-cell (CD19+ CD5+), and decreases in the NK-cell (CD3− CD16+ CD56+) cell counts and percentages. Discriminant function analysis revealed that the increase in mature B-cell (CD19+ CD5+) and the reduction in NK-cell (CD3− CD16+ CD56+) counts and percentages were the primary differences between the groups. For the cell count analysis 89% of the CFS patients were designated to be in the CFS group using this immunophenotype profile. However, 36.8% of the control subjects were classified as complying with the CFS immunophenotype cell count profile. For the percentage distribution analysis, 78% of the CFS patients were designated to be in the CFS group whilst 35.0% of the control subjects were classified as complying

TABLE 5. Immunophenotyping of the CFS Patients and Controls

Parameter	Cell Counts			Percentage Distribution		
Increased	CFS	Control	*P*	CFS	Control	*P*
CD19+CD5+	71 (7)	38 (6)	< 0.006	2.8 (0.2)	1.9 (0.2)	< 0.01
CD25+	508 (41)	348 (30)	< 0.008	19.5 (1.2)	15.5 (1.1)	< 0.03
CD19+	359 (29)	248 (27)	< 0.04	14.6 (0.9)	11.1 (1.1)	< 0.02
Decreased						
CD3− CD16+CD56+	192 (25)	266 (31)	< 0.03	8.0 (1.0)	11.4 (1.2)	< 0.02
No Change						
CD2+	2029 (119)	1963 (104)	NS	82.2 (1.0)	84.1 (1.1)	NS
CD3+	1869 (116)	1737 (101)	NS	75.6 (1.3)	74.5 (1.3)	NS
CD3+HLADR+	124 (10)	109 (14)	NS	5.2 (0.4)	4.9 (0.6)	NS
CD4+	1260 (88)	1140 (66)	NS	50.3 (1.3)	49.1 (1.8)	NS
CD4+CD45RA−	757 (67)	716 (596)	NS	31.8 (1.4)	31.2 (2.2)	NS
CD4+CD45RA+	465 (47)	422 (58)	NS	18.4 (1.4)	17.8 (1.9)	NS
CD8+	685 (45)	723 (64)	NS	28.1 (1.4)	30.5 (1.7)	NS
CD8+CD11b+	159 (23)	175 (28)	NS	6.5 (0.8)	7.2 (1.0)	NS
CD8+CD11b−	527 (45)	548 (47)	NS	21.6 (1.4)	23.3 (1.4)	NS
CD3+CD16+CD56+	96 (15)	89 (24)	NS	4.3 (0.8)	3.6 (0.8)	NS
CD4+:CD8+	1.9 (0.1)	1.7 (0.1)	NS			
Discriminant Function Analyses						
Cell Counts				**Percentage Distribution**		
Model: Wilks' $\lambda = 0.59$, $F(6,40) = 5.59$, $P < 0.0005$ **Variables** CD19+CD5+ < 0.006 CD3− CD16+CD56+ < 0.004 C25+ < 0.093				Model: Wilks' $\lambda = 0.63$, $F(6,40) = 3.86$, $P < 0.004$ **Variables** CD19+CD5+ < 0.01 CD3− CD16+CD56+ < 0.02 C25+ < 0.10		
Accuracy of prediction (% correct) CFS = 88.9% Control = 63.2% Accuracy = 78.3%				**Accuracy of prediction** (% correct) CFS = 77.8% Control = 65.0% Accuracy = 72.3%		

with the CFS immunophenotype cell percentage distribution profile. Thus, CFS patients do have alterations in immune parameters consistent with a fall in NK-cell (CD3− CD16+ CD56+) counts and percentages and an increase in B-cells and activated T-cells. However, these changes do not have a high predictability for CFS.

Association Between Biochemistry and Immune Cell Changes in the CFS Patients

Table 6 shows the correlation analysis of the association between the RNase-L ratio and the various acute phase markers and electrolytes. Data were not analysed for associations between RNase L ratio and immunophenotyping, as this will be presented separately in a larger sample group. The whole body potassium levels were associated with increases in serum calcium and reductions in the ESR. Increases in the percentage variation of the whole body potassium levels were positively associated with the %CD19+ CD5+ cells. In addition, we calculated the non-serum K^+ (= whole body potassium minus serum potassium) and the ratio of serum K^+ to the non-serum K^+ for each patient. The non-serum potassium levels were associated with the same parameters as the whole body potassium levels. However, the ratio of serum to non-serum potassium levels was not associated with the RNase L-ratio, but negatively associated with the ESR and the CD25+ count. Decreases in the serum calcium were associated with increases in the %CD4+ CD45RA− cells.

Table 7 shows the multiple regression analysis of the association between the major immune cell differences between CFS patients and controls and the serum and biochemical markers. Significantly higher RNase-L ratio and lower serum calcium levels characterized CFS-patients with decreased NK-cells. Conversely the increases in the CD19+ and CD19+ CD5+ cell levels were prominently associated with increases in the ESR and whole body potassium levels. The levels of the CD25+ cells were not associated with significant regression models and the associations with the measured variables were very weak.

DISCUSSION

More than fifty percent of the sample (51.8) showed an abnormal whole body potassium level (10% of expected normal value). Eight patients had increased, while six presented with reduced potassium levels.

TABLE 6. Correlation Analysis Between the RNase-L Ratio and the Electrolytes with the Acute Phase Reaction Markers and the Immune Cell Counts and Percentages in the CFS Patients

Parameter	RNase-L	WBK$^+$	% WBK$^+$	S K$^+$	NS K$^+$	SK$^+$:NSK$^+$	S Ca^{++}
RNase-L	-						
WBK$^+$	0.058	-					
% WBK$^+$	0.233	0.255	-				
S K$^+$	−0.015	0.379	−0.275	-			
NS K$^+$	0.057	0.999 ****	0.268	0.348	-		
S K$^+$: NS K$^+$	0.064	0.963 ****	0.355	−0.277	0.268	-	
S Ca^{++}	−0.018	0.414 *	−0.325	0.352	0.409 *	0.343	-
S Na$^+$	0.036	0.034	0.079	−0.212	0.036	0.095	−0.105
CRP	0.021	−0.105	−0.026	0.004	−0.105	−0.113	0.342
ESR	0.004	−0.439 **	0.004	−0.239	−0.433 **	−0.398 *	−0.030
CD3− CD56+ %	−0.618 ****	0.079	−0.218	0.060	0.209	0.202	0.374
CD3− CD56+	−0.510 ***	−0.018	−0.137	0.080	−0.020	−0.042	0.354
CD8+	0.401 *	−0.017	0.102	−0.051	−0.015	−0.003	0.123
% CD3+	0.388 *	0.059	0.115	0.061	0.061	0.049	−0.300
CD25+	0.050	−0.373	0.109	−0.001	−0.376	−0.399 *	−0.186
% CD19+CD5+	−0.117	0.033	0.399 *	−0.144	0.032	−0.071	−0.055
% CD4+ CD45RA−	0.163	−0.233	0.243	−0.178	−0.232	−0.200	−0.404 *

Statistical Method: Pearson product moment correlations. * = $P < 0.04$, ** = $P < 0.03$, *** = $P < 0.007$, **** = $P < 0.001$.
WBK = Whole body K$^+$, S K$^+$ = Serum K$^+$, NS K$^+$ = Non-serum K$^+$, S Ca = Serum Ca^{++}.

TABLE 7. Regression Analysis of the Association Between the Major Immune Cell Changes and Acute Phase Reaction Markers and the Electrolytes in the CFS Patients

Cell Counts	Percentage Distribution
CD3− CD56+	
Model: $R^2 = 0.379$, $F = 7.32$, $P < 0.004$ Variables 1) RNase-L R (−) $P < 0.005$ 2) Serum Ca^{++} (+) $P < 0.05$	Model: $R^2 = 0.567$, $F = 10.03$, $P < 0.0002$ Variables 1) RNase-L R (−) $P < 0.0002$ 2) Serum Ca^{++} (+) $P < 0.006$ 3) CRP (−) $P < 0.11$
CD19+	
Model: $R^2 = 0.244$, $F = 3.88$, $P < 0.04$ Variables 1) ESR (+) $P < 0.05$ 2) CRP (+) $P < 0.32$	Model: $R^2 = 0.189$, $F = 5.85$, $P < 0.03$ Variables 1) ESR (+) $P < 0.02$
CD19+CD5+	
Model: $R^2 = 0.416$, $F = 3.92$, $P < 0.02$ Variables 1) ESR (+) $P < 0.03$ 2) % Whole body K^+ (+) $P < 0.03$ 3) CRP (+) $P < 0.23$ 4) Serum Na^+ (+) $P < 0.28$	Model: $R^2 = 0.412$, $F = 3.86$, $P < 0.02$ Variables 1) ESR (+) $P < 0.02$ 2) % Whole body K^+ (+) $P < 0.02$ 3) RNase-L R (−) $P < 0.19$ 4) Serum Na^+ (+) $P < 0.31$
CD25+	
Model: $R^2 = 0.346$, $F = 2.22$, $P < 0.09$ Variables 1) Ser. K^+: Non-Ser. K^+ (−) $P < 0.04$ 2) % Whole body K^+ (+) $P < 0.15$ 3) CRP (+) $P < 0.30$ 4) Serum Na^+ (+) $P < 0.25$ 5) Serum K^+ (+) $P < 0.29$	Model: $R^2 = 0.183$, $F = 2.69$, $P < 0.09$ Variables 1) Serum Ca^{++} (−) $P < 0.07$ 2) Ser. K^+: Non-Ser. K^+ (−) $P < 0.23$

Statistical Method: Forward stepwise multiple regression.

Although we have studied only a small sample, these results suggest that whole body potassium content is likely to be abnormal in CFS-patients. However, we were not able to confirm earlier reports on significantly depleted whole body potassium content in CFS-patients compared to controls (6,7,12). Preedy and colleagues found only one whole body potassium depletion in 23 female CFS-patients (35). We conclude abnormal whole body potassium might be characteristic for subsets of, or particular disease states of Chronic Fatigue Syndrome.

Whole body potassium measurement by gamma-ray spectrometry was used. Several investigators have found this technique to be highly reliable (8,10). This technique is also successfully used to assess body composition, for example fat-free mass in a validation-study by Schaefer

and colleagues (9). However, this method has some drawbacks. Firstly, the entire potassium content of the body is not indicative of any form of potassium-distribution within the different tissues and parts of the body, and within intracellular and extra-cellular compartments. Whilst > 95% of potassium is found intra-cellularly the normal whole body potassium value does not assess hypo- or hyperkalaemia, which is the result of re-distribution of intra- and extra-cellular levels and not indicative of a change in whole body levels. Therefore, we would suggest that whole body potassium measurement is insufficient to monitor a channelopathy, especially in a complex disorder like CFS. In this study we tried to gain an insight into the variation between intra-cellular and serum potassium levels by calculating the non-serum potassium levels and the ratio of serum potassium to non-serum potassium levels. The serum potassium level did not correlate with the whole body or non-serum levels. The higher the level of serum potassium in relationship to the non-serum potassium levels was considered to be a potential indicator of a channelopathy.

These results confirm earlier reports on high prevalence of a deregulated 2-5A synthetase RNase L antiviral pathway in peripheral mononuclear cells of Chronic Fatigue Syndrome patients (3,11). Elastases and calpain (36) cleave high molecular weight ribonuclease L (80 kDa) into low molecular weight RNase L (37 kDa). Starting from the N-terminal end of the RNase L polypeptide, the first 330 amino acid sequence presents a high degree of homology with the ankyrin repeat motif. Proteolytic cleavage of 80 kDa RNase L generates ankyrin repeat motif-containing fragments. Ankyrins are a family of proteins that control numerous physiological processes by means of interactions with integral membrane proteins. For instance, ankyrin proteins are capable of associating with ABC transporters (13). In addition, since the RNase L-inhibitor (RLI) impairs the 2-5A binding to RNase L (14), RLI is almost certain to interact with the ankyrin-like part of RNase L (the 2-5A binding site is located in the ankyrin-like domain). RLI takes part of the ATP binding cassette (ABC) superfamily. Consequently, RLI binds ankyrin-like fragments in CFS-patients. When the ankyrin fragment of RNase L is released by cleavage, it interacts with the ABC-ankyrin domain interaction and deregulation of proper ABC transporters function is inevitable. Recent research revealed sequence similarity between RLI and several ABC transporters, for instance sulfonylurea receptor (SUR 1) (4). SUR 1 is an important member of ATP-sensitive potassium channels. Whilst impairment of SUR 1 functioning could be postulated to lead to extreme losses of cellular potassium, this was not

supported by the findings in this study. However, elevated plasma potassium levels directly stimulate aldosterone secretion by the adrenal cortex, which in turn increases tubular secretion to maintain the desired plasma K^+ concentration (15). This adjustment was sustained by our observation in four patients, who presented with low serum calcium levels and associated lower whole body potassium levels. Permanent monitoring of potassium distribution might be the only way to assess these changes. In addition, the ratio between the serum and the non-serum potassium might not be a valid measure of the distribution of potassium within the body. Indeed, the non-serum K^+ includes a small amount of extra-cellular potassium in the lymphatic and extra-cellular fluid in addition to intracellular potassium. K^+ efflux (and interdependent magnesium-flux) brings about a calcium-current into the cells. The latter was supported by our findings in NK-cells depleted patients. Modified Ca^{2+} homeostasis, characteristic for other pathological conditions like Alzheimer's disease and cardiac ischemia, results in disrupted regulation and excessive activation of calpain (26) and caspase-12 (27).

Immunophenotyping revealed immune-activation among our patients (both T- and B-cells). During the past decade, investigators have been highly interested in NK-cell function in Chronic Fatigue Syndrome. However, lack of consistency prevents it from being used as a diagnostic marker for CFS. Both a reduced number (28,32) and activity (29,30,34) of NK-cells have been observed. Controversially, normal or increased NK-cell functioning has been extensively reported as well (31,33,22). In our sample, we have observed a reduction in NK-cell counts, which appeared to be one of the two primary discriminate functions between patients and controls. In addition, this drop in NK-cells was very strongly associated with increases in the RNase L-ratio and decreases in serum calcium levels. The latter suggest a channelopathy in an important subset of CFS patients. However, the drops in serum calcium levels were not clearly associated with an increase in serum potassium levels.

Several authors hypothesised and confirmed the importance of activation of several ionic channels (K^+, Cl^- and Ca^{2+} channels) in the early phase of T-cell activation and proliferation (17,18). Levite and colleagues (17) investigated whether modification of the ionic composition of the extra-cellular milieu can activate human resting T-cells. They found T-cells are depolarised by elevated levels of extra-cellular potassium ions, measured by flow cytometry. Although our patient sample showed increased numbers and percentages of activated cells, no association between this marker and electrolyte balance was observed. On the other hand, initial potassium efflux (before body adjust-

ment) and calcium influx might have activated T-cells. Indeed, entrance of Ca^{2+} from the external milieu is required for T-lymphocyte activation with consequent interleukin (IL)-2 production (23-25). In addition, a recent report suggests a modification of the potassium composition of the extra-cellular milieu might be involved in activation of IL-1β (16). Indeed, K^+ efflux is a crucial coupling factor in IL-1β-converting enzyme-activation. Increased levels of IL-1 have been reported in several Chronic Fatigue Syndrome samples (19,20). However, there are just as many reports of normal values of this pro-inflammatory cytokine in CFS patients (21,22). We can conclude that at least a subset of CFS patients, or a particular stage in the disease process, is characterized by increasing levels of IL-1. We suggest this is the same subset of CFS patients who present with a channelopathy (due to the deregulated antiviral pathway). IL-1 is capable of stimulating nearly all types of humoral and cellular immune responses.

We need to interpret these results with caution. Indeed, sample size was insufficient and most of our patients were tertiary referrals. This sample was not randomly selected. However, consecutive allocation of patients seeking care must be sufficient in preventing selection-bias. RNase L-ratio, erythrocyte sedimentation rate, serum electrolytes and whole body potassium content were determined in the control subjects. In addition, current technology fails to measure intracellular potassium and calcium levels, which leaves us with indirect monitoring of channelopathy.

These observations provide preliminary evidence for a channelopathy in an subset of Chronic Fatigue Syndrome patients. To our knowledge this is the first attempt to monitor channelopathy in CFS, using electrolytes, whole body potassium, RNase L-ratio and immune cell parameters. Future research should address at calcium homeostasis and RNase L-ratio with other aspects of the disease process, to further explore channelopathy in Chronic Fatigue Syndrome.

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Gulf War Illnesses: Chemical, Biological and Radiological Exposures Resulting in Chronic Fatiguing Illnesses Can Be Identified and Treated

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ABSTRACT. Gulf War illnesses involve multiple, complex chronic signs and symptoms that loosely fit the clinical criteria for Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME) and/or Fibromyalgia Syndrome (FMS). Most Gulf War illness patients had multiple

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exposures: (a) complex chemical mixtures, including organophosphate pesticides, anti-nerve agents, carbamates and possibly nerve and blister agents, (b) radiological sources, subjecting patients to both heavy metal and radiation effects, and (c) biological sources, including bacteria and toxins and the effects of multiple vaccines. Chemically exposed patients may benefit by removing offending chemicals and depleting toxic chemicals from the patient's system and other symptomatic treatments. Patients with systemic infections, including mycoplasma and other chronic bacterial infections, can be treated with antibiotics and additional nutritional supplementation. Some patients may have their illness linked to radiological exposures, and a minority to battlefield stress. The vaccines are a prime suspect for immune dysfunction and chronic infections. The multiple, complex exposures resulted in poorly defined chronic illnesses, but subsets of Gulf War illness can be identified and effectively treated using appropriate procedures.

KEYWORDS. Gulf War Syndrome, Fibromyalgia Syndrome, Chronic Fatigue Syndrome, chemical exposures, infections, uranium, antibiotics, vaccines, chemical and biological warfare

INTRODUCTION

At least 16% (more than 100,000) of the veterans of the 1991 Persian Gulf War slowly (usually 6-18 months or more after the conflict) developed a variety of complex chronic signs and symptoms characterized by disabling fatigue, intermittent fevers, night sweats, arthralgias, myalgias, impairments in short-term memory, headaches, skin rashes, intermittent diarrhea and other gastrointestinal problems, respiratory complaints, photophobia and other visual disturbances, confusion, irritability, depression and other signs and symptoms (1-3). These illnesses have been called Gulf War Syndrome or Gulf War illnesses, and they have until recently defied appropriate diagnoses (2-4). The signs and symptoms of Gulf War illness do not easily fit into ICD-9 diagnostic categories, although they loosely fall into the category of fatiguing illnesses. Routine laboratory test results are not consistent with a single, specific diagnosis (1), often resulting in veterans not receiving a diagnosis for their condition (illness of unknown origin) or receiving a diagnosis of somatoform

disorder. Often the diagnoses assigned to patients reflect one or a small group of symptoms, but not the totality of the patients' complaints. Gulf War illness has been reported by various nations that deployed forces to the Persian Gulf War, though the incidence of reported cases in French service members is much lower than reported from other coalition nations. This last point will be discussed below.

MULTIFACTORIAL ILLNESSES OF THE GULF WAR

Although press reports often refer to illnesses associated with the Persian Gulf War as Gulf War Syndrome, there is growing awareness that Gulf War illness is a not a unique, new syndrome. First, all Gulf War illness patients do not have identical signs and symptoms (5,6). Gulf War illness appears to be a diverse collection of overlapping, persisting signs and symptoms from which several syndromes have been identified (3-6). Early reports found no common illness among veterans, or specific cause for Gulf War illness (1), but since then, subsets of Gulf War illness patients have been defined by several groups. Murray-Leisure et al. (7) called Gulf War illness Mucocutaneous-Intestinal-Rheumatic Desert Syndrome, and divided patients into three broad categories based on their major signs and symptoms (Table 1): (1) *mucocutaneous lesions*, (2) *intestinal disorders* and (3) *rheumatic illnesses*. Minor criteria included in these categories included: heartburn, rectal fissures, bleeding or hemorrhoids, lactose or meat intolerance, splenomegaly and splenic tenderness, weakness and/or chronic fatigue, headaches, muscle aches, polymyalgias, memory loss, hair loss, fevers of unknown origin, unexplained leukocytosis or neutropenia, nasal ulcers, chronic sinus or nasal congestion, atypical chest pain, new-onset asthma or chronic bronchitis, ear infections or tinnitus and dental infections.

Using factor analysis, six syndrome categories of Gulf War illness were described by Haley et al. (6) after studying a U.S. Navy Seabee (Construction Brigade) unit. The most important categories were: (4) *impaired cognition*; (5) *confusion-ataxia*; (6) *arthro-myo-neuropathy*; (7) *phobia-apraxia*; (8) *fever-adenopathy*; and (9) *weakness-incontinence*. The last three groups overlapped with groups 4 and 5, and involved weaker clustering in their analysis (6). They found that these groups differed from Post-Traumatic Stress Disorder (PTSD), depression, somatoform disorder and malingering (6). Psychological disorders such as PTSD have been diagnosed in Persian Gulf War veterans

TABLE 1. Proposed Gulf War Illness Patient Subsets

Subset or Cohort	Major Signs/Symptoms	Reference (No.)
Mucocutaneous disorders	pustular dermatitis, other signs	Murray-Leisure et al. (7)
Intestinal disorders	IBS, diarrhea, other signs	Murray-Leisure et al. (7)
Rheumatic Illnesses	polyarthralgias, night sweats, etc.	Murray-Leisure et al. (7)
Impared cognition	attention, memory, reasoning, insomnia, fatigue, depression and headaches	Haley et al. (6)
Confusion-ataxia	confusion, reasoning, disorientation, balance, depression, vertigo and impotence	Haley et al. (6)
Artho-myo-neuropathy	polyarthralgias and myalgias, fatigue, muscle fatigue, extremity paresthesias	Haley et al. (6)
Phobia-aproxia	numbness, nausea, dizziness, tingling sensations, other signs	Haley et al. (6)
Fever-adenopathy	intermittent fever, lymphadenopathy other signs	Haley et al. (6)
Weakness-incontinence	muscle weakness, dyspareunia, incontinence, other signs	Haley et al. (6)
Neuro-immune	memory, attention, ataxia, other signs	Baumzweiger and Grove (10)
PTSD	stress, depression, somatoform	Engel et al. (8)
Al-Eskan disease	pneumonitis, other signs	Korényi-Both et al. (11,40)
Chronic infections	polyarthralgias, night sweats, myalgias, other signs	Nicolson (12) Nicolson et al. (14)

(8), but this likely accounts for only a minor fraction of Gulf War illness cases. A recent psychiatric analysis indicates that the majority of Gulf War illness cases do not meet PTSD criteria (9).

Baumzweiger and Grove (10) have described Gulf War illness as *neuro-immune disorders* that involve the central, peripheral and autonomic nervous system and immune system. They attribute a major source of illness to brainstem damage and central, peripheral and cranial nerve dysfunction with demyelination. They found Gulf War illness patients to have muscle spasms, memory and attention deficits, ataxia and increased muscle tone (10).

Alternative diagnoses have been proposed for certain subsets of Gulf War illness. Some patients may have suffered sand inhalation resulting in a chronic pulmonary condition (pneumonitis) that has been called Al Eskan disease (11). Gulf War illness patients can also have chronic bacterial and viral infections as an important source of morbidity (12).

The illnesses collectively called Gulf War illness are usually not fatal (13); however, thousands of Persian Gulf War veterans have died since the war (14). Possible reasons why these deaths have not been evaluated in official studies may be the limited populations studied, and lack of in-

formation on Persian Gulf War veterans who left the Armed Forces, and died outside of military and VA hospitals (15). Estimates of between 15,000 and 25,000 or more deceased US veterans have been advanced, but the exact figures are unknown. Therefore, it is difficult to determine if Persian Gulf War veterans are at higher risk of death than non-deployed personnel. Three groups have shown, however, that Persian Gulf War veterans do have increased rates of accidental deaths compared to non-veterans (16-18). It has been postulated but not proven that this is due to neurological impairments affecting the operation of motor vehicles.

It is claimed that there are no unique illnesses associated with deployment to the Persian Gulf War-similar illness clusters (at lower rates) can be found in non-Persian Gulf War veterans deployed to Bosnia (19,20). Epidemiologic analyses of Gulf War illness have been criticized on the basis of self-reporting and self-selection, and that the veterans under study may not be representative of the larger population of veterans (19). Those criticisms notwithstanding, it remains important to characterize signs and symptoms and identify exposures, if possible, of Persian Gulf War veterans in order to find effective treatments for specific subsets of Gulf War illness patients.

Most current case definitions for Gulf War illness are symptom-based, and a consensus of different researchers has shown much higher prevalence rates of Gulf War illness in deployed than in non-deployed forces. One case control study of Persian Gulf War veterans showed higher symptom prevalence in the deployed group than in personnel from the same units that were not deployed to the Persian Gulf War (21). For certain signs and symptoms, this difference was dramatic (for example, the rate of diarrhea in the deployed group was over 13-times greater than in the non-deployed group) (21). Steele (4) showed that in three studies, Persian Gulf War-deployed forces had excess rates of 26%, 30% and 32% of Gulf War illness symptom patterns (defined as percent (%) of cases meeting the Gulf War illness case definition in deployed forces minus percent (%) of cases meeting Gulf War illness case definition in non-deployed forces). Although it has been argued that the arthralgias, fatigue, memory loss, rashes and diarrhea found in Gulf War illness patients are nonspecific and often lack a physical cause (19), this conclusion may simply be the result of inadequate workup and lack of availability of routine tests that could define the underlying organic etiologies for these conditions.

SIMILARITY OF GULF WAR ILLNESS TO CFS/ME AND FMS

In most Gulf War illness patients the variable incubation time, ranging from months to years after presumed exposure, the cyclic nature of the relapsing fevers and the other chronic signs and symptoms and their subsequent appearance in immediate family members are consistent with an organic, likely infectious process, not a psychosomatic disease or somatoform disorder (2,3,6,7). The syndromes most similar to Gulf War illness are Chronic Fatigue Syndrome (CFS) (or Myalgic Encephalomyelitis, ME) and Fibromyalgia Syndrome (FMS) (2,22). We have proposed that the signs and symptoms found in many Gulf War illness patients may be caused by chronic exposures to chemical mixtures and host responses to infectious agents, resulting in cytokine abnormalities and a variety of other responses that result in a CFS/ME- or FMS-like disorder (22,23). CFS/ME is defined by persistent, debilitating fatigue in a person who has no previous history of similar symptoms, which does not resolve with rest, and is severe enough to reduce or impair average daily activity below 50% of the patient's premorbid activity level. Patients also report at least four of the following symptoms: fever, sore throat, arthralgia, myalgia, headaches, painful lymph nodes, sleep difficulties, and neuropsychiatric complaints, such as memory loss, visual disturbances, confusion, irritability and depression (24). These signs and symptoms closely parallel those found in most cases of Gulf War illness (2,22-24). This also indicates that Gulf War illness is not a new syndrome, and it has close similarities to CFS/ME.

There are some differences between Gulf War illness and CFS/ME/FMS that may be important. Haley et al. (6) and Baumzweiger and Grove (10) have stressed that unlike most cases of CFS/ME and FMS, some cases of Gulf War illness are associated with ataxia and increased motor tone. They speculated that this may reflect cranial and peripheral nerve demyelination, brainstem inflammation, and/or limbic system involvement. Using proton magnetic resonance to measure the ratio of plasma homovanillic acid and 3-methoxy-4-hydroxyphenylgycol Haley et al. (25) found reductions in the left basal ganglia dopamine production, supporting the theory that injury to dopaminergic neurons in the basal ganglia can occur in Gulf War illness.

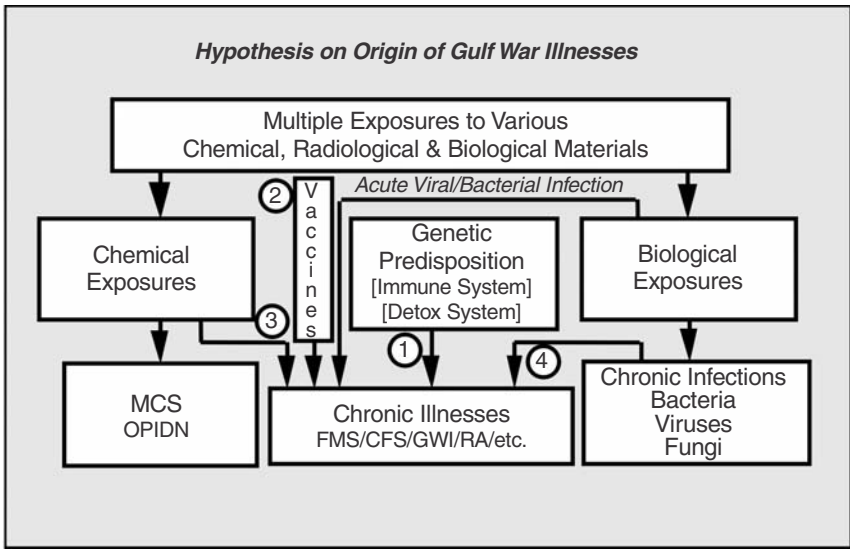
CHEMICAL EXPOSURES AND GULF WAR ILLNESS

The overlapping chronic signs and symptoms found in Gulf War illness patients could be caused by quite different types of exposures. Per-

sian Gulf War participants were exposed to chemical, radiological and/or biological agents, and most report combinations of such exposures (Figure 1) (3,6,7,10,14,23,26). Accurate diagnosis and successful treatment of Gulf War illness subsets will depend on identifying the illness-provoking exposures, because the different exposures require different methods for amelioration (22,23).

Persian Gulf War veterans were exposed to a variety of chemicals, including insecticides, such as the insect repellent N,N-dimethyl-m-toluamide, the insecticide permethrin and other organophosphates, fumes and smoke from burning oil wells, the anti-nerve agent pyridostigmine bromide, solvents used to clean equipment and a variety of other chemicals, including in some cases, possible exposures to low levels of chemical warfare agents (23). Some chemical warfare exposure may have occurred because of destruction of chemical warfare stores in factories and storage bunkers during and after the war as well as possible offensive use of chemical warfare agents (14,27). Some feel that there was no credible evidence for chemical warfare exposure (19); however, many

FIGURE 1. Hypothesis on how multiple toxic exposures, including multiple vaccines (2), chemical (3), radiological and biological (4) exposures, may have resulted in Gulf War illness in predisposed, susceptible individuals (1) [modified from Nicolson et al. (23)].



veterans have been notified by the Department of Defense of possible chemical warfare exposures.

Exposures to mixtures of toxic chemicals can result in chronic illnesses, even if the exposures are at low-levels (6,10,23,27). Such exposures can cause a wide variety of signs and symptoms, including chronic neurotoxicity and immune suppression. Abou-Donia and Wilmarth (28) found that combinations of pyridostigmine bromide, N,N-dimethyl-m-toluamide and permethrin produce neurotoxicity, diarrhea, salivation, shortness of breath, locomotor dysfunctions, tremors, and other impairments in healthy adult hens. Similarly, Moss (29) found that mixtures of chemicals similar to those encountered by Persian Gulf War veterans were much more toxic than the sum of the individual chemicals' toxicity. Although low levels of individual organophosphate chemicals may not cause signs and symptoms in exposed, non-deployed civilian workers (30), this does not negate a causal role of multiple chemical exposures in causing chronic illnesses such as Gulf War illness (19). Organophosphate-Induced Delayed Neurotoxicity (OPIDN) is an example of chronic illness that may be caused by multiple, low level chemical exposures (Figure 1) (31). Multiple Chemical Sensitivity Syndrome (MCS) has also been proposed to result from multiple low level chemical exposures (32). These syndromes can present with many of the signs and symptoms found in Gulf War illness patients, and many Gulf War illness cases may eventually be explained by complex chemical exposures (6,23,25,29-33). In chemically exposed Gulf War illness patients, memory loss, headaches, cognitive problems, severe depression, loss of concentration, vision and balance problems and chemical sensitivities, among others, typify the types of signs and symptoms characteristic of organophosphate exposures. Arguments have been advanced that such exposures do not explain Gulf War illness, or that they may only be useful for a small subset of Gulf War illness patients (19). These arguments for the most part are based on the effects of single agent exposures (19), not the multiple, complex exposures that were encountered by Persian Gulf War veterans (33). Since it is unlikely that one or even a few exposures will explain all the signs and symptoms found in Gulf War illness patients, seeking subsets or clusters of exposed patients may not be as limiting as suggested by Sartin (19). It could eventually allow practitioners to use unique combinations of treatments based on individual exposures of Persian Gulf War veterans.

The onset of signs and symptoms of Gulf War illness for most patients was between six months and two years or more after the end of the war. Slow onset of clinical signs and symptoms in chemically exposed

individuals is not unusual for OPIDN (34). Since low-level exposure to organophosphates was common in U.S. Persian Gulf War veterans, the appearance of delayed, chronic signs and symptoms similar to OPIDN could have been caused by multiple low-level exposures to pesticides, nerve agents, anti-nerve agents and/or other organophosphates (27-29,32), especially in certain subsets of Gulf War illness patients (6).

Chemical warfare agents were also present in the Persian Gulf region from the bombing of chemical warfare factories and storage facilities (and their demolition after the war), and the possible offensive use of chemical warfare agents delivered by SCUD B (SS1) missiles, aircraft or vehicles outfitted with chemical warfare sprayers, artillery shells and rockets, chemical warfare mines and other sources (23,27,31). Iraqi Armed Forces were known to have extensive stores of such weapons, and intelligence reports indicated that orders to use offensive chemical warfare agents were given. In testimony to the U.S. Congress, Army officers indicated that over 14,000 chemical warfare alarms sounded during but not before or after the air/ground offensive, and some soldiers were given medals for identifying the types of chemical warfare that were released (35). Extensive stockpiles of mustard (blister agent HN or HT), lewisite (blister agent L), sarin (nerve agent GB or GF), tabun (nerve agent GA) and other chemical warfare agents were present in the region, and an unknown quantity of these weapons were released into the atmosphere during the air campaign and by the destruction of Iraqi storage bunkers after the conflict (22,35). That low level exposure to nerve agents combined with anti-nerve agents plus other organophosphate exposures may have resulted in delayed casualties in at least some subsets of Gulf War illness is a possibility that should not be casually dismissed (19).

RADIOLOGICAL EXPOSURES AND GULF WAR ILLNESS

Depleted uranium was used extensively in the Gulf War, and it remains an important contaminant of the battlefield (14). Depleted uranium, a by-product of uranium processing, is used in armor-penetrating ammunition and in protective armor on tanks and other vehicles. Depleted uranium had been thought to contain only uranium isotopes, primarily ^{238}U (greater than 99%), and small amounts of ^{235}U and ^{234}U. However, when depleted uranium was analyzed, it was found to contain small quantities of plutonium and other isotopes, which are much more toxic and radioactive than depleted uranium itself (36). When a de-

pleted uranium penetrator hits an armored target, it ignites, and between 10% and 70% of the shell aerosolizes, forming uranium oxide particles (36). The particles that form are usually small (less than 5 μm in diameter) and due to their high density settle quickly onto vehicles, bunkers and the surrounding sand, where they can be easily inhaled, ingested or re-aerosolized.

Following contamination, the organs where depleted uranium can be found include the lungs and regional lymph nodes, kidney and bone. However, the Armed Forces Radiological Research Institute (AFRRI) also found depleted uranium in blood, liver, spleen and brain of rats injected with depleted uranium pellets (37). Pregnant rats transmitted depleted uranium to placental and fetal tissues as well. Researchers at the AFRRI further noted that "cells exposed to depleted uranium are transformed to tumorigenic cells in immune-compromised mice" (37). It is therefore possible that the immune-compromising effects of depleted uranium itself or other Persian Gulf War exposures have led to depleted uranium inducing cancer in Persian Gulf War veterans, and also that depleted uranium has produced adverse fetal effects. Studies on depleted uranium carriage should be initiated as soon as possible, to determine the prevalence of contamination, and extent of body stores of uranium and other radioactive heavy metals.

Procedures have been developed for analysis of depleted uranium metal fragments (38) and depleted uranium in urine (39). However, urine testing does not detect uranium in all body sites (36). So far, analysis of depleted uranium-contaminated Persian Gulf War veterans has not shown them to have severe signs and symptoms of Gulf War illness (39), but few Persian Gulf War veterans have been studied. Allegations that depleted uranium has led to leukemia in European troops serving in Kosovo (of whom 17 have died from leukemia) and Bosnia are being taken seriously. NATO has called for testing troops from all 19 NATO members for depleted uranium (36). In January 2001 the European Parliament called for an end to the use of all depleted uranium ammunition by NATO (36).

OTHER ENVIRONMENTAL EXPOSURES AND GULF WAR ILLNESS

In addition to the chemicals (and fumes from diesel-powered heaters) in tents and surrounding areas, soldiers were exposed to burning oil well fires and ruptured petroleum pipelines as well as fine, blowing sand.

The small size of sand particles (< 0.1 mm) and the relatively constant winds in the region probably resulted in some sand inhalation. The presence of small sand particles deep in the lungs can produce a pulmonary inflammatory disorder that can progress to pneumonitis or Al-Eskan Disease (11,40). Al-Eskan disease, characterized by reactive airways, usually presents as a pneumonitis that can eventually progress to pulmonary fibrosis, and possibly immunosuppression followed by opportunistic infections. Although it is doubtful that many Gulf War illness patients have Al-Eskan Disease, the presence of silica-induced immune suppression in some soldiers could have contributed to persisting opportunistic infections in these patients (12,14,22,27).

BIOLOGICAL EXPOSURES AND GULF WAR ILLNESS

A small number of Persian Gulf War veterans had confirmed infections with parasites, such as Malaria, Leishmaniasis and Schistosomiasis. These infections could be the cause of illnesses in additional veterans (7). Although these diagnoses may be difficult and are often not considered, characteristic signs and symptoms occur in these illnesses, and diagnostic tests are available. Infection by *Leishmania tropica*, spread by the sandfly *Phlebotomus papatasi*, can result in viscerotropic Leishmaniasis, fever, lymphadenopathy and hepatosplenomegaly (41). The prevalence of Leishmaniasis has been estimated at fewer than 100 cases in Persian Gulf War veterans.

Biological toxins were also present in the Kuwaiti Theater of Operations (23,27,42). The Iraqi Army had offensive stores of aflatoxin (*Aspergillus flavus* toxin), ricin (from *Ricinus communis* beans), *Clostridium botulinum* toxin and tricothecene mycotoxins produced by various species of fungi. Some of these toxins can be fatal in very low doses. Aflatoxin can cause delayed carcinogenic or immunosuppressive effects.

Bacterial infections are suspected in many Gulf War illness patients (12,22,23). Murray-Leisure et al. (7) have described a subset of Gulf War illness associated with cutaneous sand exposure. The illness may be caused by a transmissible agent found in sand that is endemic to the region. The risk for sand-associated illness appeared to be highest in the fall. Although no sand-associated agent has so far been identified, the slow development of the same signs and symptoms in spouses and children of veterans with Gulf War illness suggests that a slow-growing microorganism has been transferred.

Polymerase chain reaction (PCR) evidence for transmissible infectious agents has been found in Gulf War illness patients. In many cases, the veterans' immediate family members appear to have later developed similar signs and symptoms (43-45). One estimate derived from inquiries of over 1,200 Gulf War illness families indicated that approximately 77% of spouses and 65% of children born to affected veterans after the war now have the signs and symptoms of Gulf War illness (46). Not every family member developed a Gulf War-like illness, but those that did had similar signs and symptoms and similar PCR evidence of infection. Because of the apparent slow rate of transmission to immediate family members, the general public is probably not at high risk for contracting Gulf War illness from casual contact with Gulf War illness patients. However, health care personnel may be at some risk.

Evidence for infectious agents has been found in Gulf War illness patients' urine (14) and blood (22,43-45). Hyman (47) has used a microscopic technique to identify remnants of bacterial cell walls in urine, and he has successfully treated patients with several courses of broad spectrum antibiotics. We (43-45,48) and others (49) have found that most of the signs and symptoms in a large subset of Gulf War illness patients can be explained by chronic pathogenic bacterial infections, such as mycoplasma infections. In studies of over 1,500 U.S. and British veterans with Gulf War illness, approximately 40% of Gulf War illness patients have PCR evidence of such infections, compared to 6-9% in the non-deployed, healthy population (43). This has been confirmed in a large study of 1,600 veterans at over 30 VA and DoD medical centers (VA Cooperative Clinical Study Program #475). Historically, mycoplasma infections were thought to produce relatively mild diseases limited to particular tissues or organs, such as urinary tract or respiratory system (22,43). However, the mycoplasma detected in Gulf War illness patients with molecular techniques, such as *Mycoplasma fermentans*, are highly virulent, colonize a wide variety of organs and tissues, and are difficult to treat (43,50). The mycoplasma species most commonly detected in Gulf War illness, *Mycoplasma fermentans* (found in >80% of those Gulf War illness patients positive for any mycoplasma), is found intracellularly. It is unlikely that this type of infection will result in a strong antibody response, which may explain the lack of serologic evidence for these types of intracellular infections (51).

When civilian patients with CSF/ME or FMS were similarly examined for systemic mycoplasma infections about 50% of these patients were positive, indicating another link between these disorders (43). In contrast to Gulf War illness, however, several species of mycoplasma

other than *M. fermentans* were found in higher percentages of CSF/ME and FMS patients than Gulf War illness patients (43,49,52).

Approximately one-half of Gulf War illness patients also show fragile chromosomes that are more easily degraded by cellular nucleases, resulting in release of characteristic nucleotide fragments (53), but this might be due to the action of intracellular bacteria that are known to release chromosome-damaging chemicals (50,54). Similarly, the finding of activation of the coagulation system in Gulf War illness patients could also be related to chronic infections that cause coagulation disturbances (55).

A few other chronic infections have been found in Gulf War illness patients. In contrast to an early official report (56), we have found preliminary evidence for *Brucella* infections in some Gulf War illness cases. Inhalation of *Brucella melitensis* can cause many but not all of the signs and symptoms of Gulf War illness. Another bacterial infection found in small numbers of cases includes Q Fever (57), caused by *Coxiella burnetii*.

MULTIPLE VACCINES AND GULF WAR ILLNESS

A possible source for immune disturbances and chronic infections found in Gulf War illness patients is the multiple vaccines that were administered close together around the time of deployment to the Gulf. Unwin et al. (20) and Cherry et al. (58) found a strong association between Gulf War illness and the multiple (including biological warfare) vaccines that were administered to British Persian Gulf War veterans. Unwin et al. (20) and Goss Gilroy (59) also noted an association specifically with anthrax vaccines and Gulf War illness symptoms in British and Canadian veterans. Steele (4) found a three-fold increased incidence of Gulf War illness in *nondeployed* veterans from Kansas who had been vaccinated in preparation for deployment, compared to nondeployed, non-vaccinated veterans. Mahan et al. (26) found a two-fold increased incidence of Gulf War illness symptoms in U.S. veterans who recalled they had received anthrax vaccinations at the time of the Gulf War, versus those who thought they had not.

In the United States, Gulf War illness signs and symptoms have developed in personnel who recently received the anthrax vaccine. On some military bases this has resulted in chronic illnesses in as many as 7-10% of personnel receiving the vaccine (60). The chronic signs and symptoms associated with anthrax vaccination are similar, if not identi-

cal, to those found in Gulf War illness patients, suggesting that at least some of the chronic illnesses suffered by veterans of the Persian Gulf War were caused by vaccines (60). Undetectable microorganism contaminants in vaccines could have resulted in illness, and may have been more likely to do so in those with compromised immune systems. This could include individuals with depleted uranium or chemical exposures, or personnel who received multiple vaccines in a short period of time. Since contamination with mycoplasma has been found in commercial vaccines (61), the vaccines used in the Persian Gulf War should be considered as a possible source of the chronic infections found in Gulf War illness (60).

TREATMENT OF GULF WAR ILLNESS

Treatment of Gulf War illness should follow from knowledge of the types of exposures encountered around the time of the Persian Gulf War. For example, the treatment of chemically sensitive patients involves removal of offending chemicals from the patients' environment, and may also include methods to remove chemicals from the patients' depot sites, and other treatments (23,62-65). Chemically exposed patients can be extremely sensitive to a variety of commonly encountered chemicals, including perfumes and air fresheners, petrochemical fumes, chlorine, cleaning solutions and solvents. They may also be very sensitive to certain foods, and special diets can be necessary. In some cases, cutaneous contact with certain substances can cause strong reactions.

Gulf War illness patients with MCS or OPIDN may benefit from dry saunas (63), as well as magnesium sulfate-hydrogen peroxide baths (66). Toxic substances may be removed through a program of heat depuration, physical therapy, nutritional supplementation, and in some cases other therapies might be employed (62-65). In addition to heat, exercise and diet, a variety of medications may alleviate some symptoms in Gulf War illness patients. Some patients have benefited from anti-anxiety, anti-depressant and anti-inflammatory drugs (10), but this may not be beneficial for other Gulf War illness patients, especially those with chronic infections (22,63) or with MCS.

Amelioration of depleted uranium carriage depends on reducing the body burden of heavy metals by chelation, and surgical removal of shrapnel, combined with nutritional strategies. However, it must be recognized that the actual composition of depleted uranium and the extent of its toxicity remain to be determined. The extent of troop contamina-

tion also remains unknown and should be determined. Although chelation therapy has been proposed for depleted uranium contamination, the effectiveness of chelation for depleted uranium removal is uncertain, particularly for exposures that took place years earlier.

Chronic infections can be treated with the appropriate antibiotics. Treatment with antibiotics can result in improvement and even recovery in patients made ill by bacteria or mycoplasma, such as *M. fermentans* (22,43-45). The recommended treatments for systemic mycoplasma infections require long-term antibiotic therapy (22), because few patients recover after only a few weeks or months of treatment. This may be a reflection of the intracellular locations of most mycoplasma, the slow-growing nature of these microorganisms, or their inherent resistance to antibiotics (50). Once our patients recovered and were able to return to pre-illness levels of activity, mycoplasma gene sequences could no longer be detected in their leukocytes. These clinical responses were not due to placebo effects, because administration of antibiotics that are not effective against mycoplasma infections, such as penicillin, resulted in patients becoming more, not less, symptomatic. Interestingly, CFS/ME, FMS and Gulf War illness patients with systemic infections that slowly recover on antibiotic therapy become less environmentally sensitive, suggesting that their immune systems may be returning to pre-illness states. If such patients had illnesses that were caused by stress or solely by chemical exposures, they would not respond to the recommended antibiotics and slowly recover. In addition, if such treatments were just suppressing autoimmune activity, then patients should have relapsed after the treatments were discontinued (50).

We and others (67) have found abnormal levels of certain substances (thyroid hormone, aldosterone, cortisol, vitamin B12) in some Persian Gulf War patients, possibly due to autoimmune attack on endocrine tissues. These levels should be monitored and appropriately supplemented.

FINAL COMMENTS ON GULF WAR ILLNESS

Because of the relatively nondescript, widespread, chronic signs and symptoms of Gulf War illness, it has defied a simple case definition. Various authors have described Gulf War illness as a set of distinct syndromes. However, Gulf War illness may simply be a complex collection of overlapping chronic illnesses caused by multiple toxic chemical, radiological and biological exposures, including vaccines.

Interestingly, the French Ministry of Defense reported very few Gulf War illness cases (68). During the Persian Gulf War the French forces did not use vaccines as a primary defense against Iraqi BW, and they did not use anti-nerve agents extensively as a defense against Iraqi chemical warfare agents (69). Instead, they used controlled environments, prophylactic antibiotics to counter BW agents, and depended on protective suits to counter chemical warfare agents (27,60,69). Finally, efforts are being made to determine the relative effectiveness of these very different chemical and biological prophylactic and treatment strategies used by different nations (69). The French Ministry of Defense has been urged to investigate the role of vaccinations, obtained by small numbers of French troops while serving with U.S. and British forces, in French soldiers who have now developed Gulf War illness (60,68).

Recent attention to the role of chemical and radiological exposures, hormonal deficiencies, and infections with microorganisms (some possibly originating from the vaccines used in the Persian Gulf War), in Gulf War illness patient subsets, has allowed investigators to successfully treat Gulf War illness cases. Because this approach to Gulf War illness has not been widely used, we hope to encourage other clinicians to extensively evaluate and successfully treat ill Persian Gulf War veterans and their families.

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