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# **Handbook of Chronic Fatigue Syndrome**

**Leonard A. Jason**

**Patricia A. Fennell**

**Renée R. Taylor**

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## CHAPTER 3

# The Complexities of Diagnosis

BYRON HYDE

THE VIEWS IN this chapter are those of the author and do not necessarily reflect those of the editors of this book. Since 1985, I have restricted my practice to the investigation of patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) and the underlying causes of their illnesses. Whenever possible, I spend an entire day and part of the next examining the patient, and this has allowed me to observe anomalies that might elude other physicians. I then embark on a systematic mapping of the patient's structures, systems, and organs. Only then do I reach a conclusion about the disease process that I am trying to understand and uncover. Few physicians have such a luxury of time. Because this protocol is costly for the medical system under which physicians generally practice, I do not suggest that the readers of this chapter must follow it. It might lead to financial difficulties if the physician is a fee-for-service physician or practices within a medical group that dictates the amount of time to be spent on consultations.

My methodology has produced certain views and findings that may be inconsistent with many in this field. The opinions expressed here are, in large part, a result of my own clinical experience and are not derived from empirical findings from controlled research studies. At the Nightingale Research Foundation, Bonnie Cameron, Lydia Neilson, and I did a survey of 2,000 patients in 1990 – 1994 that has informed many of my opinions, but the study was not published.

### INVESTIGATION OF ME/CFS

In our text, *The Clinical and Scientific Basis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome* (Hyde, Goldstein, & Levine, 1992), I distinguished between ME and CFS. More recently, and specifically at the biennial CFS Symposium held in Seattle in 2001, some individuals, dissatisfied with the name chronic fatigue syndrome, suggested changing it to myalgic encephalomyelitis or some variation of that name. This would be unwise. Although ME and CFS share many characteristics, the titles often represent two distinct groups of illnesses.

#### *MYALGIC ENCEPHALOMYELITIS (ME)*

The term *myalgic encephalomyelitis* was based on clinical descriptions of an illness that has occurred both sporadically among the general population and in clusters, or epidemics, usually in hospitals or schools. Over 60 such epidemics have been described in the medical literature (Acheson, 1992; Henderson & Shelokov, 1992; Hyde, 1992) since Sandy Gilliam, Assistant Surgeon General of the United States and later Dean of Medicine at Johns Hopkins, first

described the 1934 epidemic in the Los Angeles County General Hospital (1938). B. Sigurdsson et al. (1950) in Iceland, D. A. Henderson, and A. Shelokov, in the United States (1959a, 1959b); A. Wallis, in 1955, and A. M. Ramsay, in 1988, and John Richardson, in England (1992); and P. Behan, in Scotland (Behan & Behan, 1988; Behan, Behan, & Bell, 1985), have all added to this growing literature. This group of illnesses has been given many names, but these have distilled down to myalgic encephalomyelitis (ME), a term used primarily in the United Kingdom, Canada, and Australia.

These various clinical descriptions include these characteristics:

- A sporadic and epidemic postinfectious illness most frequently occurring in the late summer or early autumn, with an incubation period from 4 to 7 days. The epidemic illness is most commonly acquired in hospitals, schools, or domiciliary institutions at a time when an increase of similar sporadic illness occurs among the general population. Although the illness is seen in diverse occupations, health care workers, teachers, and students are the most commonly affected.
- The epidemic illnesses have been associated with infrequent deaths involving CNS (central nervous system) changes. Many of these changes have been subcortical brain changes. Deaths in sporadic cases have been rare but have been associated with acute cardiac arrest, with no signs of coronary disease, and frequently suicide. Deaths other than suicide are uncommon.
- Onset of the primary ME illness usually follows abruptly during the recovery phase of an often banal infection (if an infection is noted at all) or within 4 to 20 days of an immunization. Frequently one observes the onset of an ME-like illness after multiple infectious episodes. The primary infectious illness and the ME illness do not resemble each other. Most infectious illnesses are described as upper respiratory tract, flu-like, gastrointestinal and, less commonly, hepatic illness or pneumonia. Traumatic incidents associated with minor infectious illness or travel to foreign countries. These associations often follow within 30 days of a series of immunizations.
- ME illness in adults is associated with measurable changes in the CNS and autonomic function and at times injury to the cardiovascular, endocrine, and other organs and systems. It is described as (1) a systemic illness often of subnormal temperatures; (2) marked muscle fatigability; (3) an acute onset of CNS changes of memory impairment, mood changes, sleep disorders, irritability, and reactive depression; (4) involvement of the autonomic nervous system resulting in tachycardia, coldness of the extremities, urinary frequency, bowel changes, pallor, and sweats; (5) diffuse and variable involvement of the CNS leading to severe headaches, visual problems, ataxia, weakness, cramps, and sensory changes; (6) muscular and neck pain, acute fleeting spasmodic pain and tenderness, and myalgia.
- In children in the acute phase, there is depression with weeping, significant loss of energy, retardation and impairment of thought and memory process, disorders of sleep, behavioral disorders, acute onset of school problems, often of a serious nature, with a reluctance to attend school, and with a significant weight loss. Children are usually diagnosed as hysterical or school phobic.
- The initial period of illness lasts from weeks to up to two years and tends to be more severe. During this period, the patient either recovers, remains, or relapses in a chronic

phase of variable severity. The chronic phase is often sufficient to prevent return to school or work for either long periods or permanently.

- Dr. Michael Goldberg, of Tarzana, California, believes that this illness often results in children being rejected, abused, and abandoned to the street or to juvenile criminal activity. Dr. John Richardson (1992), of Newcastle, and others have documented significant associated cardiac and cardiovascular injury as well as other organ injuries associated with the usual CNS and autonomic changes in this group of patients. Dr. Seymour Grufferman (1992), of Pittsburgh, has described an increased incidence of malignancies, often lymphomatous, associated with individuals in clusters of ME/CFS. A similar finding was initially described in some of the patients in the Lake Tahoe epidemic (Daugherty et al., 1991; Peterson et al., 1992).

All ME descriptions were concerned with chronic or recurrent acute onset illnesses. The ME descriptions deal with primarily CNS and autonomic changes and, at times, with easy fatigability and with poor or delayed recovery of CNS or muscular abilities. Although ME clinical descriptions noted the infectious onset and infrequently the postimmunization history of ME illness, neither pharyngitis nor involvement of lymph nodes was ever mentioned in any of the clinical descriptions of the actual chronic illness manifestations.

Host factors are important in ME. At the time of the initial illness, the patient often appears to be either temporarily or chronically immune-compromised by one or more of the following:

- Exhaustion from overwork or night shifts
- Repetitive infectious disease
- Recent immunization
- Significant illness or trauma
- Toxic chemical exposure

As in all diseases, there is a significant variation in the degree and range of injury. Those who are least injured often simply return to school or work and operate at a lower productivity and escape diagnosis. Those who are most injured or die are easily recognized at disease onset or shortly after as CNS, cardiovascular, or organ injury. Because of their overwhelming illness and the specificity of the end-organ injury, they are never diagnosed as ME except in epidemic or cluster situations. Overwhelming fatigue is often a feature of the chronic illness phase (Fukuda et al., 1994). After a few months, however, this profound fatigue often changes and some patients begin to feel normal until they are challenged by any physical, intellectual, emotional, or sensory stress. In this new phase, the patient has rapid fatigability and poor recovery after any stressor. These patients begin to feel they inhabit a body and mind significantly different from usual, and sometimes they panic. The adult patient with moderate to major illness rarely recovers totally, but usually does improve (Joyce, Hotopf, & Wessely, 1997). It is an unacceptable improvement. Those adults who are still significantly ill at two years can still improve but only a few ever return to any degree of normal function. Unlike adults, the majority of children and adolescents, even those seriously injured, who have proper care and are in a positive economic environment, tend to recover substantially or at least improve significantly over time (Marshall, 1999).

## *CHRONIC FATIGUE SYNDROME (CFS)*

The physician and patient alike should remember that CFS is *not* a disease. It is a chronic fatigue state as described in four definitions starting with that published by Dr. Gary Holmes of the CDC and others in 1988 (Holmes, Kaplan, Gantz, et al., 1988; Holmes, Kaplan, Schonberger, et al., 1988). The definition created by Lloyd, Hickie, Boughton, Spencer, and Wakefield (1990) is also widely used in Australia. There are two subsequent definitions. The Oxford definition of 1991 (Sharpe et al., 1991) and the 1994 NIH/CDC definitions (Fukuda et al., 1994) are basically, with a few modifications, copies of the first definition. Where the one essential characteristic of ME is acquired CNS dysfunction, that of CFS is primarily chronic fatigue. By assumption, this CFS fatigue can be acquired abruptly or gradually. Secondary symptoms and signs were then added to this primary fatigue anomaly. None of these secondary symptoms is individually essential for the definition and few are scientifically testable. Despite the list of signs and symptoms and test exclusions in these definitions, patients who conform to any of these four CFS definitions may still have an undiagnosed major illness, certain of which are potentially treatable. Although the authors of these definitions have repeatedly stated that they are defining a syndrome and not a specific disease, patient, physician, and insurer alike have tended to treat this syndrome as a specific disease or illness, with at times a potentially specific treatment and a specific outcome. This has resulted in much confusion, and many physicians are now diagnosing CFS as though it were a specific illness. They either refer the patient to pharmaceutical, psychiatric, psychological, or social treatment or simply say, "You have CFS and nothing can be done about it."

The CFS definitions have another curiosity. If in any CFS patient, any major organ or system injury or disease is discovered, the patient is removed from the definition. The CFS definitions were written in such a manner that CFS becomes like a desert mirage: The closer you approach, the faster it disappears and the more problematic it becomes.

### **SIGNIFICANT DIFFERENCES BETWEEN ME AND CFS**

Though the symptoms of CFS resemble those of ME, the differences are so significant that they would exclude ME patients from the 1988 and 1994 CDC diagnoses of CFS. The following features of ME separate it from CFS:

- The epidemic characteristics
- The known incubation period
- The acute onset
- The associated organ pathology, particularly cardiac.
- Infrequent deaths with pathological CNS changes.
- Neurological signs in the acute and sometimes chronic phases.
- The specific involvement of the autonomic nervous system.
- The frequent subnormal patient temperature.
- The fact that chronic fatigue is not an essential characteristic of the chronic phase of ME.

However, there are four essential differences between ME and CFS that are perhaps more important than any of the preceding differences:

1. No one in composing the two CDC definitions told anyone not to investigate the CFS patients during the first 6 months of illness; they simply stated that the CFS is characterized by an illness of 6 or more months of chronic fatigue. Undoubtedly, it was unintentional. Yet obviously CFS following infectious disease begins in day one of the first 6 months or even in the days before this initial period. Researchers into CFS have simply avoided that essential area. The inception of an illness is always the most fertile area of research into cause and pathology.
2. Organ disease in CFS has been avoided. By definition, it does not occur. If significant primary or secondary organ disease occurs, then this would be a cause of the fatigue and the illness would not be CFS (Fukuda et al., 1994).
3. The inventors of the second CDC CFS definition laid out certain guideline examinations (Fukuda et al., 1994). They never stated that no other testing should be done, but for all purposes, these very preliminary tests have been used for inclusion guidelines in CFS research papers. Research physicians have apparently forgotten that we do not know what CFS is from a pathophysiological basis. For this reason, not only have most physicians avoided exhaustive testing but many have decried exhaustive testing as foolish.
4. This is the most important essential difference. Nowhere in any of the four definitions of CFS is there a discussion of acute versus gradual onset illness. This has allowed physicians to include any patient who fits the 1988 or 1994 or U.K. definitional characteristics into the CFS illness spectrum. Because none of these definitions mentions gradual onset CFS disease, gradual onset patients, as a group, not only fit the four definitions but also totally obstruct CFS as a disease category. The reason for this statement is simple. Gradual onset CFS frequently represents non-diagnosed major disease or pathophysiological anomaly. Many patients with a diagnosis of CFS today have non-diagnosed major diseases. These patients warp any statistical or scientific examination of the CFS patient. Most of the patients I have seen from Canada, the United States, or from the United Kingdom with gradual onset CFS illness have non-diagnosed major medical illness or anomaly. This fourth essential difference defines the cornerstone of investigation of much CFS.

### **PREMISES CONCERNING THE PATIENT AND THE DISEASE ENTITY**

The patient with the diagnosis of ME/CFS is chronically and potentially seriously ill with (1) a poorly understood illness of a pathophysiological nature or (2) a missed classical disease entity. The typical patient has seen many excellent physicians, who have failed to discover the cause of the patient's illness other than to variously call it ME or CFS, psychiatric illness, somatization, or more charitably, "I simply do not know." These physicians have repeatedly performed many tests but have generally failed to find any significant or substantial indication of cause or nature of the patient's disease.

At least some of the patients with an initial diagnosis of *gradual onset* ME or CFS have another and potentially treatable classical disease or anomaly. These ME/CFS patients require a total investigation and essentially a total body mapping to understand the pathophysiology of their illness and to discover what other physicians may have missed. In many instances, patients

appear to know more about ME/CFS than their physician and in fact have directed their own investigation under the directional guidance of a kind and supportive clinician.

These patient-directed investigations usually jump from one trendy test of little value to another consuming vast amounts of funds and time. Rarely, however, do the physician and patient end up with any substantial scientifically supportable disease entity or diagnosis other than that with which they started – ME/CFS. One can assume that many of the patient's physicians have spent the proverbial 8 minutes that an average North American or British physician spends with the average patient. Likewise, most internists will have spent 40 minutes doing a classical history and physical that can generally detect obvious acute disease or advanced disease of a progressive nature, but is usually irrelevant in understanding a chronic pathophysiological illness.

I assume that none of the patient's illnesses is due to a psychiatric cause until I have completed my investigation. In the end, although these patients may have significant anxiety and problems caused by loss of income, social status, and meaning, less than 5% have any significant psychiatric illness. Initially in 1985 to 1990, I was able to unravel the causative disease or illness in the ME/CFS group in no more than 10% to 20% of the patients I examined. By 2000, I was able to discover the major elements of the underlying disease pathophysiology in 70% to 80% of the patients I examined. Each year, my success ratio has improved. Because of this, I believe that the 20% to 30% failure rate in defining the pathophysiology of this group is due to my own deficiencies as a physician and/or the deficiencies of the available technologies. One should not blame patients for their illness or jump too casually to a psychiatric or sociological diagnosis.

For me, a patient with an initial diagnosis of ME/CFS can be a gold mine of disease, missed injuries, physical and physiological anomalies, and genetic curiosities.

## **PHILOSOPHY AND ECONOMIC ETHICS OF INVESTIGATION**

I base my philosophy of examination and testing of ME/CFS patients on the following considerations:

- The majority of ME/CFS patients who seek medical assistance in my practice tend to be middle-income individuals or professionals. Many have been unable to work for years. The patient's loss of income for one year usually represents more than \$30,000, and I have seen patients who have lost an income in excess of \$500,000 per year. These individuals tend to range in age between 20 and 40 and are in the prime of their work life when they first fall ill. If they cannot return to work, the gross income loss to themselves, an insurer, or the state – or simply the loss of their productive life – can often reach \$1 million to \$15 million.
- The technological component of a reasonably complete investigation and body mapping rarely should cost more than \$10,000. The term *body mapping* is an idiom I adapted from another profession. Prior to becoming a physician, I worked as a geophysicist, and to evaluate an anomaly, it was necessary to first map the terrain in detail with surveying and geophysical tools to measure the size, depth, and nature of the anomaly. Diamond drilling and core analysis often followed the initial measurements. I helped discover several mines that people had often walked over without even realizing what they had missed.

The investigation of an ME/CFS patient is similar to the research leading to the discovery of a gold or nickel mine or an oil deposit. Before you can know and understand what anomaly you are dealing with, it is sometimes necessary to do a total body mapping. This may cost approximately \$10,000. At this point, many physicians and insurers will throw up their hands in exasperation. They cannot justify spending such a considerable sum to investigate a patient who, in their judgment, has an obviously psychiatric/somatic illness or is simply too lazy to return to work and has been properly investigated by several reputable physicians.

- The majority of ME/CFS patients cost themselves, or the medical system in which they operate, far more than \$10,000 over the course of their illness in a totally nonstructured series of haphazard investigations. Even compared with a year's income, \$10,000 represents a fraction of the patient's or employer's loss. When compared with a lifetime loss of \$1 million to \$15 million, such an investigation cost is paltry.
- Although individual patients may know a great deal more than I do about some particular aspect of some particular disease or pathology, they are not physicians. Nor is the patient usually trained as a physician, and rarely does the patient understand the rigors of scientific medicine. Some physicians, in attempting to earn a reasonable living in these economically challenging times, have also relinquished their investigational skills. It is not for nothing that medical training is so prolonged. Medicine is a difficult profession; medical investigation is a difficult pursuit; the investigational physician can never know enough or have enough tools or instruments to measure everything that needs to be measured. Faced with the challenge of ME/CFS illness, no physician can presume to understand the pathophysiology of this group of illnesses; particularly after only an hour with the patient and a few standard tests.
- The chronic ME/CFS patient deserves, at least once, a complete investigation that includes mapping of (1) body structures, (2) organs, and (3) systems. Where little or nothing is initially discovered, the same physician should repeat this investigation after a few years. Over time, even chronic disease tends to be progressive and more visible to investigation. Also, physician skills and professional knowledge continue to improve. Patients routinely arrive in my office telling me they have had a complete workup, but few of these patients have had what I consider to be even basic investigation.
- The investigation of a known illness such as heart valve disease or a brain tumor is relatively simple and can be completed with an economy of tests and examinations. A chronic disease process that is poorly defined or is of unknown origin requires a different approach.

### **THE PHILOSOPHY OF TREATING ME/CFS DISEASE**

Though ME/CFS usually represents significant disease processes, the underlying pathophysiologies or physical anomalies causing these processes are so varied that it is unreasonable and perhaps even dangerous to suggest or embark on any uniform treatment.

Although CFS has been defined as a syndrome, patient, physician, and even government agencies have increasingly tended to speak about CFS as a specific disease entity with a potentially specific treatment or treatments. Whether this suggested treatment protocol employs pharmaceuticals, cognitive or physical retraining, or alternative medications and treatments,

these treatment modalities and philosophies are not medically justifiable and are often potentially dangerous to the patient.

In the past two centuries, the development of Western medicine was based on autopsy, physiology, pathology, and reproducible tests. The goals were to define and, where possible, treat the causes and/or the pathophysiology of the disease process. This philosophy of modern Western medicine has been the basis for almost all of the great medical cures and treatments for specific diseases during the nineteenth and twentieth centuries. To date, however, this approach has largely been missing in the investigation and understanding of ME/CFS disease.

There has been an immoral intervention by the insurance industry into the philosophy of physicians and health workers treating this group of disease entities. This corporate insurance company intervention has used the mechanism of sponsoring medical symposiums to produce a uniform, insurance-friendly policy. Insurance companies have reputedly placed large numbers of rheumatologists and specific subspecialists in a given area under a significant annual retainer, injuring not only patient access but also negatively influencing other physicians who may not be aware of this economic relationship.

## **INFLUENTIAL FACTORS IN TREATMENT**

The definitions of myalgic encephalomyelitis (ME), chronic fatigue syndrome (CFS), and fibromyalgia have colored all investigations of this illness group. The definitions of myalgic encephalomyelitis and chronic fatigue syndrome describe what may originally have been the same disease, but the differing definitions have caused confusion.

### *FIBROMYALGIA AND VASCULAR PAIN*

Both ME and CFS patients may have associated pain that includes fibromyalgia (Taylor, Friedberg, & Jason, 2001). Some have no associated pain dysfunction. The pain syndromes, and there are many, vary in intensity and tend to be worse in the first years of illness and after the patient has encountered physical, intellectual, sensory, or emotional stressors. Although some researchers have found specific chemical changes in the spinal fluid of these patients, and others have demonstrated subcortical SPECT (single photon emission computed tomography) anomalies (Goldstein, 1992), it is likely that in the future measurable findings may be found in the posterior columns and posterior root ganglia. If physiological spinal cord changes occur, they have not been subjected to scientific scrutiny because specific noninvasive testing modalities are not yet available.

Instead of following neurological pathways, some of these pain mechanisms are probably vascular. If this is true, this may suggest injury to the autonomic system. Any physician subjecting this category of patient to a thallium chemical cardiac stress test will know that many of these patients experience severe incapacitating pain that sometimes lasts for days, even several weeks. Although I do not know if there is a CNS or spinal basis to these pain phenomena, the paradoxical thallium test would suggest a vascular basis to the pain dysfunction in this group of patients.

Raynaud's phenomenon is a common secondary occurrence in both ME/CFS and fibromyalgia. When significant fibromyalgia occurs in conjunction with ME or CFS, the chronic disability tends to be additive.

### *ACUTE AND GRADUAL ONSET ILLNESS*

I tend to arbitrarily place acute onset patients in the ME category and the gradual onset in the CFS category. This arbitrary categorization is not entirely satisfactory. Some patients have no idea if their illness started abruptly or gradually. Even so, overlap in these two groups makes it an imperfect analysis. Remember, a patient with ME is a patient whose primary disease is CNS change, and this is measurable. The primary disease of a patient with CFS is fatigue, and fatigue is neither definable nor measurable.

The gradual onset CFS group is of particular concern to me. It is in this group that occult disease, whether malignant, space occupying, organ pathology, or vascular injury of the CNS or cardiac system, is most frequently observed. A typical ME-like history can often be due to a malignancy (Richardson, 1992) or other pathology that should be located as soon as possible. Whether a patient fell ill abruptly or gradually, or has been ill for many years, is no excuse not to search for a potentially treatable malignancy or a cardiac, vascular, or other organ illness. Patients with ME/CFS are not immune from developing other illnesses that may be potentially terminal.

### *THE RATIONALE FOR INVESTIGATION*

*Scientific Medicine* The tradition of Western scientific medicine is to isolate the cause of the illness, measure it, and specifically treat that cause if possible. Without being able to understand and measure the nature and degree of the underlying injury or disease, it is impossible to measure the effectiveness of any treatment. Some causes of ME/CFS-like illness are eminently treatable, and effective treatment may allow the patient to go back to work or school.

*Understanding* Patients want to know and have the right to know what has happened to them.

*Insurance Indemnity* Some, if not most, insurance companies do not accept the diagnosis of ME or CFS as a basis for disability even if the patient is permanently bedridden or confined to a wheelchair. The physician must be able to demonstrate the underlying injury to a court, if need be, to assist the truly disabled patient in claiming a disability pension. Although this does not treat the disease, at times it can materially restore the disabled individual to acceptable financial stability, without which life often becomes intolerable.

*Financial and Social Loss* The majority of patients with ME/CFS-type illness tend to be professionals or individuals with an above-average education and a successful career, who may forfeit significant income because of work loss in their lifetime (Anderson & Ferrans, 1997). Each of these patients requires a complete clinical, laboratory, and scientific investigation at least once. Although I have seen some patients who were charged \$20,000 to \$100,000 for \$3,000 worth of tests, a complete technical investigation should cost less than \$10,000. Many physicians

and corporate organizations think that the state or their company cannot afford to investigate a patient in such depth, even though the state or insurance company has no difficulty in paying that patient \$10,000 to \$20,000 a year or more in social benefits if the disability is accepted. A thorough evaluation of the patient could help eliminate this problem of rational accountability.

## **THE IN-DEPTH EVALUATION**

### *PATIENT HISTORY*

In addition to the regular history, prior to the first visit, I have the patient provide a full extended family genealogical health history going back three or even four generations and including siblings of each generation, all of their known illnesses, and cause of death. Patients who know their birth parents usually can obtain this history. Frequently, mapping this genetic history suggests or even reveals the source of the CFS patient's real illness. Patients with ME sometimes have a curious history. I often find an excess of recurring and major neurological illnesses in previous generations. Even though paralytic poliomyelitis was relatively rare, it is common to find one or more polio victims in the family tree. I have often wondered if these patients do not suffer from a specific immunological dysfunction to neuropathic viruses.

### *GEOGRAPHIC HISTORY: A POTENTIAL INVESTIGATIONAL BLIND SPOT*

Patients, as they should be, are very concerned about toxic chemical exposure as a cause of their illness. Physicians and governments pay lip service to this concern, but perhaps because of lack of technology, I have found little supportive evidence to substantiate toxic chemical exposure as a cause for chronic ME/CFS (Crowley, Nelson, & Stovin, 1957; Shelokov, Habel, Verder, & Welch, 1957). However, patients who have a history of being raised on an active twentieth-century farm or a village with no central water supply are potentially victims of well water toxic chemical exposure.

Well water is normally only routinely examined for bacteria, and in my experience, farm and village well water is almost never examined for pesticides or herbicides. In villages and towns that rely on local or central well water, whose source is near a major farm area, chemical factory, or dry cleaner, the users of this water may have been subjected to toxic chemical exposure in their water for decades. This type of exposure can lead to a gradual immune breakdown. Hair or serum analysis may not demonstrate these old exposures. Many of these toxins are lipophilic and a fat biopsy (liposuction) should be considered in this group. Since pesticides, herbicides, and all organophosphates accumulate in fat and the brain is essentially fat, the brain should be considered to be a natural reservoir of these chemicals. The brain, of course, is also the major immune-regulating organ of the body. Since we cannot routinely do brain biopsies, analysis of samples of liposuction fat may help to identify toxic levels of these chemicals.

## *PSYCHIATRIC HISTORY*

Patients frequently hide their family psychiatric history. Often I am assured that there is no psychiatric history, and then after an exhaustive examination, I find no physical causes for the patient's illness. Patients with ME/CFS with no observable pathology are very infrequent. I then go back and ask specific questions of each family member. Infrequently, I find a severe psychiatric history. Having said this, I doubt if more than 2% to 5% of ME/CFS patients have a primary psychiatric history. Why should there be fewer psychiatric patients in this group? The patients that I see, particularly in the acute onset group, are primarily professional middle-class individuals. They have worked hard for years to further their careers, and most persons with major initial psychiatric illness would have simply failed to achieve this success.

## *PHYSICAL EXAMINATION*

The severity of ME/CFS illness is not usually accompanied by significant observable physical changes in the regular physical examination. This causes some physicians to assume that there is no major disease present in patients with ME/CFS. Yet most male patients I have seen have never had a rectal or women a vaginal exam, and almost none have ever had anyone look into their nasal passages.

The physical examination does not start on the examining table. My physical examination often starts with the moment the patient gets out of a car to come into my office. Severely ill patients seldom come since they cannot get out of bed or handle the nine steps to my office. These patients I see only in their homes. The mild cases, who keep working or going to school, are rarely if ever seen by a physician. I have an advantage in often being able to see the patient from my window. Typical moderate to moderately severe ME patients often cannot get out of a car normally. Patients who have driven any distance often physically lift their legs out, first one leg then the other, hold onto the car door frame, and struggle out. Their upper leg flexors are unusually weak. Sometimes they have short-term foot drop and cannot raise their foot. I have a simple gate catch that a child can open instantly. I have seen patients work for several minutes without being able to open the latch. A sign on my outside door says "ring and enter," and often the patient simply rings and stands there. Once inside, the patient often goes down the steps one at a time, one foot leading while holding firmly on to the banister.

During the daylong examination, +I often accompany patients for tests in the hospital simply to observe them. They frequently do not walk normally; they get lost in their purses or wallets attempting to find their identification. Walking with these patients is often like walking with a tortoise. They can be slow, clumsy, sometimes walking with a wide leg stance. Some have a movement disorder that does not conform to the classical Parkinson or upper motor neuron disorders. These patients have obvious CNS injury but simply do not fit into neat categories.

Initially, patients are often excited about seeing me, their adrenaline pumping, and a physician who saw some of these patients for only up to an hour would reasonably conclude that they were high-energy patients with nothing wrong. This is misleading. During the course of a day's examination, the patient may change from a brighter than normal person to one who resembles a blank-faced zombie, a patient who can talk and walk only with difficulty or not at

all. Sometimes their voices become scanning, and they begin verbally to stumble. Normally, I take the patient to lunch. This helps me diagnose the infrequent bulimics. Sometimes patients are fine all day, but when I see them on the second day, they have often, in physical and intellectual terms, gone to pieces. A one-hour physical examination will rarely pick up ME/CFS pathology.

*Oral Temperature* Prior to the office visit, I have patients take a temperature reading at specific times, 4 times a day for three days, and also ask them to have a healthy friend of the same age and sex provide a similar temperature series for comparison. This is not a good test due to the variation of procedures and menstrual cycles, but the patient with acute onset ME/CFS frequently has a substantially subnormal temperature. In 15 years of examining chronic ME or CFS patients in Canada, the United Kingdom, and Australia, and in CFS clinics in the United States, I have found an elevated temperature on only two or three occasions. The significance of elevated temperature in the CFS definition eludes me. Patients have subnormal or normal temperatures.

*Cervical and Axillary Glands* The initial CDC case definition for CFS suggested as a physical criterion, "Palpable or tender cervical and axillary lymph nodes" (Holmes et al., 1988). Few of the signatories of that definitional paper were actually clinicians who had ever seen any ME/CFS patients on a regular basis. The Oxford Group corrected that and simply stated, "There are no clinical signs characteristic of the condition" (Sharpe et al., 1991, p. 119).

ME/CFS patients frequently have surface hypersensitivity or pain syndromes, but since 1985, I have rarely found significant cervical or axillary glands in an ME/CFS patient. Sometimes they do have painful elliptical swellings. When they occur, they can be quite large but are fleeting. One is located above and to the right of the left mammary gland. Often if you ask, the patient will go to that point but say it "isn't there today." Over the years, several ME/CFS patients have told me that they have had their left breast biopsied at this exact site for possible malignancy and nothing was found.

Another location is a row of these elliptical swellings in the left axilla at the chest wall muscle edge. These may come out during the first few years of illness at any time and later when the patient is tired. They are subcutaneous and tender and in severe cases cause a bruise or discoloration over the spot. You can roll them under the ball of the finger. They are exquisitely painful. They are never constant.

In the past, I have had two patients biopsied and found that there were no abnormal lymph nodes but a bundle of histiocytes. Dr. J. Gordon Parish demonstrated to me that often the subcutaneous anterior upper legs are also "lumpy" in these patients. If you find enlarged lymph glands in the cervical or axillary areas, look for other causes than ME/CFS.

### *OTHER PHYSICAL FINDINGS*

Of the following 20 abnormal findings in these patients, none is strong enough to excite most internists or neurologists. The findings are not usual in a healthy patient, however, and many are not specific to ME/CFS. There tend to be more findings in the early illness, but some persist and appear to increase during the course of the day:

1. Ghastly pallor of face with frequent lupus-like submaxillary mask

2. Parkinsonian rigidity of facial expression and altered walk
3. Scanning, disjointed speech, or reversals
4. Nasal passage obstruction and inflamed areas around tonsillar pillars
5. Sicca syndrome of conjunctiva and mucous membranes
6. Drenching sweats often reported, but seen most frequently later in day
7. Raynaud's phenomenon with infrequent loss of normal fingerprint
8. Unequal pupils and contrary pupil reaction to light
9. Tongue tremor
10. Rare Adie's pupil with absent patella reflex
11. Positive modified Romberg
12. Frequent equivocal Babinski/plantar reflex on one side
13. Cogwheel leg raising and lowering motion that increases during the day
14. Frequently reported muscle twitching; infrequently seen in office after exercise
15. Sometimes marked falling pulse pressure in arterial pressures taken first when prone, then sitting, then standing
16. Rapid heart rate on minor activity such as standing
17. Associated fibromyalgia
18. Unusual sensitivity of cervical vertebrae area
19. Laryngeal stridor when fatigued
20. Nodular thyroid

### *EXAMINING TEST RESULTS*

The patient may have had a large number of tests and physician reports. These should be examined in detail. Sometimes these tests disclose the clues to diagnosis that have been missed. Never simply accept an MRI, PET (positron emission tomography), SPECT, or X-ray report that states it is normal. When possible, review the film or printout yourself. If you feel uncomfortable doing that, find a specialist who can assist you. Recently, I saw a patient who had been seen at a major U.S. neurological clinic in Boston for three days at a cost of \$12,000. Part of this examination included an MRI that was read as normal. When I asked a neuroradiologist to check this for me, he stated there was a significant lateral shift of the ventricles and to look for a malignancy or atrophic condition.

Some ME/CFS patients (e.g., patients with spherocytosis and sickle cell anemia), tend to have an unusually low erythrocyte sedimentation rate (ESR). Elevation of ESR may suggest an active inflammatory disease. Persistent elevation may indicate an acute infection, a malignancy, or a missed rheumatoid disease. ESR is an inexpensive nonspecific test, and some medical organizations impugn it. All high ESR patients should be rechecked for chronic infectious, malignant, and rheumatoid disease. Physicians should always repeat all abnormal tests before coming to any conclusions since it may be a false abnormal.

### *ORDERING TESTS*

*Routine Blood and Chemical Tests* I ask patients to have their own physician do locally any tests that have not already been done. It saves patients both time and money. Most physicians are

happy to assist, but a few simply refuse, perhaps because they believe that the patient has no measurable physical illness. For example, glucose tolerance tests are increasingly frowned on by significant members of the medical community as being expensive and unnecessary in the evaluation of diabetes mellitus. These physicians are correct; however, a glucose tolerance test does more than simply define diabetes – it can demonstrate *hypoglycemia*, that much maligned illness that has passed out of vogue. I always do insulin levels with my glucose tolerance tests and frequently discover derangement of insulin response in some ME/CFS patients.

The following tests should be considered for all ME/CFS patients:

1. Routine CBC with sedimentation, blood smear, ferritin, and IBC. Many patients have a significant ferritin and IBC anomaly with normal Hb and Ht.
2. Eosinophil count.
3. Before ordering B12, check with the patient, who often is consuming vast amounts of B12 in vitamin combinations that will give abnormal highs.
4. Urinalysis and culture.
5. Immune and protein electrophoresis.
6. Immune panel only if it can be done in the immediate vicinity.
7. TSH, FT3, FT4, and thyroid antibody tests.
8. Thyroid ultrasound must be done on all patients. In the past two years, I have diagnosed six cases of thyroid malignancy with ultrasound. Often, these patients have normal serum thyroid tests.
9. Parathyroid Ab, Ca, and Ph.
10. Complete lipid profile.
11. HIV 1 and 2, treponema antibodies, hepatitis B (surface and core ab) and C, toxoplasmosis, histoplasmosis, Lyme disease.
12. Tuberculin skin test for all patients who have not received immunization.
13. Stools for parasites, ova, and blood x 3.
14. SGOT (AST), SGPT (ALT), bilirubin, BUN, uric acid.
15. ANA and rheumatoid battery if suggested.
16. PA and lateral X-ray of chest and X-ray of sella tursica and sinuses.
17. Fasting and 3-hour glucose and glucose tolerance if indicated.
18. Smooth and striated muscle ab and mitochondria ab.
19. Street drug profile to include cannabis, cocaine, LSD, and so on.
20. Prostate specific antigen (PSA) on all males over 25.

*Thyroid Disease* It is well known that the thyroid is one of the essential glands that regulate energy and temperature, and it is equally well known that ME/CFS patients tend to have both energy and temperature dysregulation. For this reason, I not only do free T4 and TSH on all patients but also do thyroid antibody tests. Even with major thyroid disease, the TSH may be normal. TSH appears to have a diurnal rhythm as do cortisol levels; TSH may vary from week to week. Even with all of these tests returning as normal, I do a thyroid ultrasound on all ME/CFS patients. I then do a needle biopsy on all hypervascular nodules found or solitary nodules over 1 cm in diameter. Thyroid ultrasound is noninvasive and inexpensive. I examined one patient who had been seen by over 20 physicians in the United States and found a malignant thyroid. In the past 18 months, I have discovered 5 ME/CFS patients with a malignant thyroid requiring thyroidectomy and three with missed Hashimoto's thyroiditis. Curiously, each of these patients

with a malignant thyroid also had a history of spending much of the day before a computer terminal at work. I do not know if the computer terminal association is more than a simple fortuitous association. These patients with significant thyroid pathology as found on ultrasound and biopsy often have relatively normal TSH, free T4 and, less frequently, relatively normal thyroid antibody tests. Their thyroid pathology, however, is only part of a general autoimmune dysfunction, certainly involving the CNS but undoubtedly other areas as well. NeuroSPECT scans in these patients, as well as their immune tests also tend to be grossly abnormal. Once the thyroid problem is successfully treated, the patient occasionally gets better, but more often does not. The SPECT immune anomalies tend to persist.

*Discussion* For some, this list of tests would already appear to be excessive. However, I cannot count the times that I have found abnormal thyroid and parathyroid function in this group of patients. HIV does not normally cause a fatigue syndrome except in its final stages and I rarely find HIV or positive treponema tests in this group. I may find one HIV every two years, but every year I discover several unexpected cases of either hepatitis B or C in ME/CFS patients. Some of these patients are sexually active and have seen 20 physicians who have not ordered these tests or discovered these illnesses.

Low levels of elevated ANA are almost to be expected in many ME/CFS patients, particularly early in their illness. Over time, the ANA levels tend to fall in those who do not go on to develop clinical rheumatoid disease. I occasionally find scleroderma antibodies in patients with clearly defined Sicca syndrome. At least 50% of my patients have either significantly abnormal immune or, much less frequently, abnormal protein electrophoresis that sometimes leads to the diagnosis of specific diseases.

If immune tests are not done on the same day the blood sample is taken, the levels will not be correct. These tests are very expensive and serve little purpose for either patient or physician unless they are part of a total investigation and are performed in an expert laboratory. Immune abnormalities should be repeated with a suitable hiatus to make sure they do not reflect an acute infectious anomaly. I almost never find evidence of street drugs in these patients. However, it is amazing how few patients have had a chest X-ray in the previous decade, and at times I find major lung, mediastinum, and cardiac pathology. Although gross observable pituitary anomalies on routine X-ray occur with increased frequency in this group, they tend to be few and far between. One should be aware in doing pituitary or adrenal tests that birth control medication can cause variables in this group of tests that at first would appear pathological. I recently examined a beautiful teenage girl with a moon-shaped face, hair changes, and marked striae who had been treated with corticosteroids by her physician for adrenal dysfunction. She had all the usual corticosteroid side effects and all that was behind it was that she was on birth control pills. There was no adrenal dysfunction.

I have now seen several children previously diagnosed with CFS who proved simply to have intestinal parasites. Once treated, these patients immediately bounced back to health. A positive eosinophil count is a good indication to look for parasites.

I do a PSA on every male above 25. I had a very good friend, a wonderful cardiologist, who in a jovial manner told me one day he had CFS. I asked if I could examine him and he declined saying it would get better. His CFS was discovered, too late, to be a prostatic carcinoma. If there is a family history of prostate disease, I do a transrectal ultrasound as well as a PSA, which may pick up prostate malignancy later than one would want to.

Most physicians would not find the preceding series of tests all that alarming unless they believe that the ME/CFS group of illnesses is an invented phenomenon. This simple set of tests may lead to other tests that define the disease of at least 25% of the group who are mistakenly diagnosed with ME/CFS. Without this baseline, it is pointless to do more expensive tests since the tests already mentioned may suggest the illness. Even physicians who agree that this set of tests is reasonable may balk at additional tests.

## *TWO CAUTIONS*

*Testing for Legal Purposes* Although I have seen patients win disability claims with one good proof, it is better to be prepared to give at least three significant pieces of evidence demonstrating proof of disability. Then if one proof is discounted, your multiple evidence may be sufficient to win over the judge. Some investigations may take up to two years. If your patient's disability case will possibly go to court before then, you should urge the patient to first obtain a lawyer experienced in insurance law to advise both the patient and yourself. A lawyer will make sure that the insurance company does not invalidate the claim by creating delays. Some states in the United States and all insurance companies have widely different approaches to disability claimants. Your patient requires necessary legal protection from the onset. Do not delay this essential step of making sure your patient has a lawyer before you spend significant time on investigation. It does patients no good to find that they are chronically ill with little chance of recovery if they then also lose the right to claim on their disability insurance. An expert lawyer may be as essential to the welfare of these patients as an expert investigation.

*Lumbar Puncture* There are two important points to be aware of in doing a lumbar puncture. The most important is that during the early days or weeks of the disease, the patient may have a significant increase in intracranial pressure. *Always use a small-bore needle.* Do not forget to take the spinal fluid pressure reading as well as the fluid. Since 1985, I have seen two patients where the physician's use of a large-bore needle for the puncture resulted in the brain stem being herniated into the upper spinal canal causing a permanent iatrogenic partial paralysis. The second point to remember is that many patients with acute onset ME/CFS may demonstrate IgG oligoclonal bands in their spinal fluid. These do not usually go on to develop multiple sclerosis (MS). Do not frighten or advise patients prematurely that they have MS without meeting the full obligatory MS criteria.

## *VIRAL CAUSES OF ACUTE ONSET ME OR CFS*

Thousands of physicians in North America, Europe, and Austral-Asia have expended considerable funds to study the possible viral causes of ME/CFS. Some physicians have their pet theories, but none has been proven to be correct. Viral antibody tests are a particular waste of time and money since all humans are a virtual bank of hundreds if not thousands of viruses, some of whose antibodies are reactivated with a wide range of viral challenges. Only in epidemic situations where a rising viral antibody titer can be captured is it worthwhile to do antibody tests. Since acute onset disease has an incubation period of 4 to 7 days, usually at the lower limit, it makes little sense to ruminate about herpes virus 6 with an incubation of approximately 10 to 12

days or EBV with an incubation period of around 40 days. Even with a positive SPECT as a marker, we have not found a consistent viral cause. But having said this, I should add that we have never found any chronic viral infection by PCR on any patient with definite gradual onset CFS.

In acute onset ME patients with clear SPECT changes, however, we have had positive enterovirus PCR in about 10% of these patients for up to 3 years post-illness onset. The enterovirus that we have found has often been a new, nonlisted enterovirus similar to ECHO 25. This positive finding begins to drop at 2 years, and we have not found an elevation after 3 years. We have not found this virus in normal healthy controls with the exception of two normal patients who had received massive blood transfusions. Another curious feature is that many acute onset ME patients have incredibly high polio 1, 2, or 3 antibody levels. They obviously do not have polio, but perhaps some of the viruses that cause acute onset ME are similar in nature to poliovirus. Even so, 10% of acute onset illness represents about 5% of the total number of ME/CFS cases. If it is an answer, it is only a partial answer at best. Enterovirus PCR is also very difficult to perform and many North American labs do not have the experience to perform this test accurately. I noticed that a physician for the National Institutes of Health (NIH) was doing their enterovirus analysis in Scotland, where I was doing mine. The difference is that the NIH physician was not screening patients for acute and gradual on-set illness or investigating them in any detail to remove patients with major missed disease.

### *DOPPLER ULTRASOUND AND ECHOCARDIOGRAMS*

The most important tests that I do are Doppler scans and echocardiograms. They are more productive than MRIs or almost any other group of tests in uncovering pathology in ME/CFS patients. The following tests, which I do on all patients, pick up another 25% of the underlying cause of disease:

- Visual carotid Doppler from aortic arch
- Visual transcranial Doppler to include vertebral and basilar arteries
- Thyroid ultrasound
- Echocardiogram and Doppler

*Discussion* Dr. John Richardson from Newcastle upon Tyne has followed ME patients in Durham and Northumberland counties of the United Kingdom for three to four generations. I am aware of no other physician in the world with such a historic view of ME patients. He has repeatedly demonstrated that many ME patients go on to develop structural heart injury. The injury is usually valvular or related to pericardial effusion, and although most settle down, some do not and may develop myopathy. So I started to look at the hearts of these patients.

I have found that during the first year of acute onset ME/CFS disability, the incidence of pericardial effusion is unusually high. This seems to settle down with no apparent short-term problem, and after a year, the cases of pericardial fluid decrease considerably. However, the incidence of valvular disease in people in their 30s and 40s appears to be higher than in the normal population. When I find a significant valvular injury, I then repeat the echocardiogram yearly, and more frequently if the patient develops shortness of breath. I have observed several cases of elevated right heart pressure, significant septal defects, and increased myocardial wall

thickening. Some who have had the injured valve replaced have miraculously returned to normal health. Are these incidental findings? I do not know, but Dr. Richardson has identified more than several hundred cardiopathies in his ME practice. I had two heart valve replacements in this group in the past year out of a total of 50 new patients.

*Carotid and Transcranial Doppler* Few physicians investigating ME/CFS employ the visual carotid and transcranial Doppler. This is a major error. It is a relatively inexpensive and totally safe procedure that does things no other type of test can do. On rare occasions, you will find aneurysms and subclavian steal anomaly with this test. Carotid atherosclerosis – sometimes substantial – is often found in patients with lipid dysfunction. This is a treatable condition and can be part of the cause of a CNS fatigue syndrome. You may say that any internist or cardiologist can pick up carotid pathology with a stethoscope, but few do who do not have an office Doppler. The carotid scan is also essential if you wish to do a transcranial Doppler

I examined a patient from the United States who had been diagnosed as having CFS in two major U.S. CFS clinics. She was given alternative medications and told to return in one year. She had complete obstruction of the vertebral basilar arteries and approximately 80% and 90% obstruction in either carotid. I was amazed that she was still alive. She was successfully operated on in Boston and her CFS has significantly improved.

The transcranial Doppler is not a perfect test. Patients with small foramen magnum space are difficult to visualize. But it will demonstrate high level internal carotid and other arterial obstruction that is beyond the normal range of a stethoscope. Only rarely do I get the chance to investigate posttraumatic mitral valve area (MVA) patients who develop an acute fatigue syndrome where personality or intellectual change has given rise to the diagnosis of CFS. In two of the past four such patients, I have demonstrated small subcortical arterial blowouts that had been missed by neurologists and that were possibly the cause of their pathophysiology.

In patients with ME/CFS, it is possible to demonstrate spasmodic disease of both major and smaller arteries with no typical evidence of migraine. This arterial pathology may be the end organ underlying cause of some ME patients' illness. Often MRIs and MRAs miss such arterial physiological pathology. Why? The technology of the MRA consists of a receiving computer revolving around the brain that may only give a picture of the maximum arterial diameter. In other words, what you see on the MRA is not reality but one view of reality. With the transcranial Doppler, the operator actually watches and films the kinetic movement of the arteries within the brain and can measure the velocity of the blood flow. Not only can you see these arteries move; if they are in spasm, you can observe this as well. Like ME/CFS muscles, ME brains are sometimes in significant pathological spasm. This knowledge may lead to more effective treatments of ME/CFS disease. Arterial spasm may account for some, but not all, of the SPECT changes that are routinely seen in ME patients.

I often find partial or complete vertebral or basilar artery obstruction. Frequently, I find left middle cerebral artery spasm or obstruction and, less frequently, frontal artery spasm in ME/CFS patients who do not report a migraine history. Left middle cerebral arterial field hypoperfusion is typical of ME.

## *ULTRASOUND*

Consider using the following ultrasound scans:

1. Abdominal and pelvic organs and aorta
2. Prostatic ultrasound
3. Femoral and popliteal arteries in patients with leg pain

*Discussion* Like many physicians, I have never been able to palpate a spleen except in the most extreme cases, such as you find in malaria. (We don't have much malaria in Canada.) Like most physicians, however, I can pick up an enlarged spleen with ultrasound. Early on in the ME/CFS disease, you will find a small number of enlarged spleens, but this becomes infrequent as the disease progresses past one year. Fatty infiltration of the liver is regularly seen and is usually dietary. I infrequently discover metastatic cancer (CA) in the liver. It is rare to uncover other major organ pathology to account for CFS. Organ pathology is more common in women, where too frequently we have found ovarian and pelvic tumors – some malignant (Billy Wilder's wife was diagnosed with CFS in 1989 and nothing was done for her condition; she subsequently died of ovarian cancer). Ultrasound is a fairly inexpensive noninvasive type of testing, and I do it on every patient. I routinely find pelvic pathology in as many as 30% of females. In the past three years, I have found only three pelvic malignancies – fortunately, the discoveries saved two patients' lives.

#### *FURTHER EXAMINATION OF THE HEART AND CARDIOVASCULAR SYSTEM*

The following tests are recommended:

1. 24-hour Holter monitor
2. Stress ECG or chemical stress test
3. Cardiac PET scan
4. Circulating red blood cell and serum volume

*Discussion* I routinely use a Holter monitor on all patients. The cardiologist often reports these as normal. *Do not trust this report.* What the cardiologist or computer is basing the report on is the number of ischemic events. However, read the lowest heart rate at night, and note that it sometimes falls to the low 40s. Though this may be normal in an athlete, it is not in a sedentary ME/CFS patient. For a patient who is not active all day long and has an average heart rate that flirts with 100 beats per minute or more, you know that this is not normal. These abnormal tests, however, are often reported as normal. We routinely pick up significant abnormal ischemic events. Similarly, as high as 10% of our patients have coronary artery disease. This is verified on stress test. So often do I find significant ischemic hearts in this group despite their young age that I now do stress tests only in the cardiology department.

Patients with ME/CFS frequently cannot do exercise tests, and so I then do chemical testing as a second best. Several of our patients have reacted severely to the chemical test with excruciating pain. This is not true angina, and although the pain sometimes ceases as soon as the chemical is stopped and the antidote given, sometimes it persists for weeks after the procedure with no sign of coronary artery disease. I do not understand this phenomenon, but it is obviously vascular. The cardiologists state that this pain does not occur with the same frequency in non-ME/CFS patients and now recognize it as a sign of pain or fibromyalgia associated with ME/CFS.

The cardiologists routinely do cardiac PET scans on my patients with positive Holters and to date have only very rarely found ischemic muscle pathology. Dr. Peter Behan from Glasgow has demonstrated routine abnormal myocardial PET scans on his ME patients (Behan & Behan, 1988; Behan et al., 1985). Once again, I have not figured out why he can get these and our cardiac unit cannot. I do circulating blood volume on all patients. Dr. David Bell, a pediatrician in New York, was the first to demonstrate this useful test. It serves little purpose for most physicians, however, unless they test all patients with the same protocol and the nuclear medicine department has experience with this test. In our hospital, we find a wide variety of circulatory changes in relation to surface volume. I have some ME patients with a circulating red blood cell volume less than 50% of expected and a very large number with the range of 60% to 70%. What this test means is that blood is pooling somewhere in the body and that this blood is probably not available for the brain. In effect, there may be a reduced perfusion of oxygen and a reduced perfusion of insulin, growth factor, and other essential nutrients and chemical triggers in these patients.

When blood flow to the heart decreases sufficiently, the organism has an increased risk of death. Accordingly, the human body operates in part with pressoreceptors that protect and maintain heart blood supply. When blood flow decreases, pressoreceptors decrease blood flow to noncardiac organs and shunt blood to the heart to maintain life. This, of course, robs those areas of the body that are not essential for maintaining life and means the brain, muscles, and peripheral circulation are placed in physiological difficulty. This may cause much of the symptoms in ME/CFS patients. It probably suggests an intrinsic autonomic failure in these patients. We see SPECT changes in the subcortical brain responsible in part for maintaining reasonable autonomic function. I *repeat*, this test – circulating blood volume – is not useful except in labs with technicians who can do it correctly, in patients who follow a precise protocol, and in relationship to the complete assessment. Many patients want to run off and obtain one and then say, "This proves I have ME or CFS." Neither this test nor any single test proves the presence of disease.

### *DIAGNOSTIC TESTS OF MYALGIC ENCEPHALOMYELITIS*

Consider the following tests:

1. SPECT
2. Xenon SPECT
3. PET
4. Neuropsychological Testing

*Discussion* The primary diagnostic criterion for ME is acquired CNS change. We have excellent tools for measuring these physiological and neuropsychological CNS changes: SPECT, xenon SPECT, PET, and neuropsychological testing. CFS patients may not have any of these findings, particularly if their illness is due to some of the problems previously discussed.

Ever since Dr. Jay Goldstein asked Dr. Ishmael Mena, Nuclear Radiologist then at Harbor-UCLA Medical Center, to measure brain dysfunction in an ME/CFS patient's brain with his SPECT scan (Goldstein, 1992; Mena, 1991), it has been one of the most important tests for me in the evaluation of ME.

I do not describe a patient as having ME unless there is an abnormal SPECT. If the SPECT is normal, I often repeat it along with xenon SPECT. If the brain scans remain normal, I conclude that it is unlikely to be ME. I then refer to the patient as a CFS patient and search for other causes of the fatigue syndrome. Few people listened to Drs. Goldstein and Mena at the time. The problem was not with the physicians but that the CFS definition did not fit their discovery. Their discovery did precisely fit ME.

What is a SPECT? This is a computer-driven technology that demonstrates the microcirculation of the terminal arterioles in the brain and/or the function of areas of the individual brain cells. An ME patient has an abnormal brain SPECT. In this technology, there is a microcirculatory phase and a cellular phase. To my knowledge, the technology cannot distinguish whether the problem is in the brain cell or in the microcirculation, or both, unless a two-phase test is performed.

In some cases of MRI spectrography of arm muscle of ME patients, it has been shown that because of an abnormal buildup of normal metabolites, the muscle cell actually shuts down to prevent cell death. This cell field shutdown is probably what is happening to the true ME patient's cell physiology in the brain. It probably explains in part the so-called brain fog and the dysfunction after the brain is stressed. It probably also explains muscle dysfunction. In legal cases, I also attempt to send the patient for xenon scan, which demonstrates the significant shutdown of the brain after exercise. I also send the patient for PET scans to obtain confirmatory changes in this completely different technology. Neither xenon SPECT nor PET is necessary except for research or legal cases, but both give a great deal of information about the pathophysiology of this disease to the knowledgeable physician. Xenon SPECT scans are almost impossible to find.

In visual terms, SPECT changes come down to two basic types of radical changes to brain physiology. The typical SPECT change in an ME patient is a decreased perfusion in the cortex in the area of the left middle cerebral artery and the branches leading to the posterior parietal lobes. This can also affect the anterior cerebral artery on the same side. Less commonly, this pathophysiology occurs on both sides involving both left and right middle cerebral arteries and anterior frontal arteries. Still less frequently, the findings are noted primarily on the right. To my knowledge, no one has published on whether there is an increased right brain abnormality in left-handed patients. Among other functions, the left middle cerebral artery covers the areas of the brain for visual and auditory recognition and interpretation. Decreased function of this CNS area creates a significant memory problem in that the patient has difficulty laying down new information and retrieving old information in the presence of added information (any external sensory stimuli/stress).

Often there are also significant changes in the subcortical regions, specifically in the brain stem, cerebellum, and basal ganglia area. Some authorities have identified fibromyalgia changes in the immediate subcortical areas; however, I have not verified this. Another finding that we frequently discover is sometimes referred to as a *vasculitis* pattern (the "itis" part of myalgic encephalomyelitis). This change is identical to what one finds in a patient with HIV dementia. The pattern is irregular and basic SPECT structures appear distorted. Patients with this vasculitis pattern are some of our most severely affected. Once again, the referring physician needs to actually see the scan and be able to read it since the neuroradiologist often only does a partial report. The brain is a big area and you have to be able to ask the neuroradiologist to check specific areas for anomalies. This is where your ability to read these scans is important. There are also problems with the SPECT equipment. Unless the neuroradiologist has a reasonably up-to-

date SPECT scanner and appropriate columneter and associated software, the results may simply not be as good as they could be. SPECT scans are only helpful in physicians who understand them; then they can be essential in the diagnosis. They should always be done in conjunction with a carotid and transcranial Doppler to rule out obstructive arterial disease, which is not uncommon in these patients.

### *NEUROPSYCHOLOGICAL TESTING*

This is a complex type of testing, and a physician should attempt to locate an experienced neuropsychologist without ties to the insurance industry. Most neuropsychologists today are employed by the insurance industry, and if they find too much pathology, I suspect that they are no longer engaged. Do not be fooled by a negative insurance-paid neuropsychological report; psychologists whose primary training is not neuropsychology prepare many of these reports. Discussion of this area would require an expert such as Sheila Bastien.

### *EXPENSIVE TESTS*

The following tests require sophisticated, costly equipment:

1. Magnetic resonance imaging
2. Magnetic resonance angiography
3. MRI pectography
4. Tilt table
5. Sleep function

*Magnetic Resonance Imaging (MRI)* An MRI is what every patient wants, but which few patients need. But the physician may require the added certainty of the information it can provide. The MRI does not necessarily demonstrate the disease pathophysiology of an ME patient, but it may demonstrate the cause of a CFS patient's illness (Hyde, Biddle, & McNamara, 1992). Many physicians simply do an MRI of a patient and almost nothing else. When it comes back as normal, the physician or the insurance company then tells such patients that nothing is wrong with their CNS and so they can go back to work or school. It is a mistaken belief that a brain dysfunction can be seen in an MRI evaluation. Generally an MRI is useful for one purpose, to demonstrate abnormal anatomy. Some neuroradiologists do not read MRIs very well, particularly if they read the scans and not the computer module. On the computer, you can blow up areas in doubt and also obtain different images. Nevertheless, MRI is changing. It would be useful if all MRIs had the computer software to print out the volume of the entire brain and its subdivisions individually – the ventricles and certain brain organs such as the cerebellum. This capability is technically possible and exists in some centers. The brain areas could be measured for later comparison to facilitate observing rate of atrophy or increase of ventricular volume. There are changes on some ME/CFS brains but what I use the MRI for is simply to rule out malignancy, ventricular or pituitary changes, and brain atrophy not seen clearly on a CT scan or routine radiography. This is important since I infrequently discover both MS and non-MS demyelinating and calcified areas suggestive of a previous focal infection.

I have a patient who had a profound sleep and memory disturbance diagnosed as ME/CFS after returning from Africa. The instant I stopped talking to her to answer the telephone, she would fall asleep in my office. One day, I let her sleep from in the morning until 5 in the evening simply to see when she would wake up. She didn't. So I woke her up at 5 o'clock to tell her it was time to go home. I sat there all day doing paperwork and she didn't once awaken. She was negative for all of the usual sleep-inducing illnesses common in Africa and had a totally normal MRI. The diagnostic clue in her history was that the African town in which she had stayed was overrun by millions of rats and she had been bitten. I made a presumptive diagnosis of Weil's disease with a CNS infection involving the sleep centers.

She gradually recovered over a period of 2 to 3 years only to fall ill again with a stroke and renewed sleep dysfunction. The repeat MRI at that time demonstrated calcification of the substantia nigra area of the basal ganglia and this Yon Economo-like disease affecting the basal ganglia probably contributed to her profound sleep problem. Just because an MRI or any test is normal does not mean that it will stay normal. The patient's visible symptoms are sometimes a better barometer that something is wrong than the best tests that a scientist can devise.

*Magnetic Resonance Angiography (MRA)* An MRA is simply an MRI scan that highlights the arterial blood supply. An MRA demonstrates arterial obstruction but does not show the arterial activity that can sometimes be seen on transcranial Doppler. I have not done many of these, but they have been useful in posttraumatic cases of ME/CFS (Hyde, Biddle, et al., 1992). I have found more pathology in the less expensive transcranial Dopplers than in MRAs.

*MRI Spectography* Because these capabilities are few and far between, I have not used them except in the United Kingdom, in Oxford. MRI spectography has demonstrated the abnormal buildup of metabolic by-products during normal activity of ME patients muscle cells (Hyde, Biddle, et al., 1992). When this occurs, the cell effectively shuts down to prevent cell destruction. This is seen graphically when Olympic runners' muscles seize, often just before the finishing line. This may be what is happening in the brain cells that tend to shut down when stressed by normal activity.

*Tilt Table Examination* I frequently find gross abnormalities in ME/CFS patients with this test. A circulating blood volume and a complete cardiac investigation should be done first. This is not a test to undertake lightly since the patient's heart sometimes stops and may have to be restarted. This test should only be done in major hospital centers in the presence of an appropriate physician where such emergency capabilities can be instituted. With this test, I have found significant pathology in about 10% of ME/CFS patients suggesting significant autonomic disease. There is, however, a wide discrepancy in the protocols of this type of testing, and so it is difficult to compare results. Some physicians strap the patient onto the table preventing movement that would induce circulation and others leave the patient relatively free allowing some movement-induced circulation.

*Sleep Function Testing* This is a useful and important test for all patients. Many ME/CFS patients have sleep dysfunction that tends to be worse in the first year or two of illness. Often involuntary movements and pain spasms provoke this dysfunction, and the patient simply cannot obtain the necessary sleep. The chronicity of the disease poses a possible danger in placing these patients on long-term analgesics or hypnotics because the patient rapidly becomes accustomed to

them while the overall pain and movement-induced sleep dysfunction persists. However, it is sometimes possible to correct obstructive sleep apnea when it is found.

### *PROS AND CONS OF ELECTROENCEPHALOGRAMS (EEGs) AND QUANTITATIVE ELECTROENCEPHALOGRAMS (QEEGs)*

In court, I am sometimes asked why I did not do an EEG. There are major problems with EEGs. Although they are sometimes positive during the first few weeks of illness, they are rarely performed at this time unless the patients complain of severe headache during epidemics. An EEG only records activity on the outer millimeter of the brain. Almost all ME patients tend to have involuntary movement disorders that are worse when the patient first falls ill and tend to decrease with time. Yet the neurologist reading an EEG almost never states an EEG IS abnormal unless the patient has an active seizure disorder or is brain dead. An average neurologist will spend 10 minutes or much less reading an EEG, whereas it would take a PhD student weeks to measure any abnormalities in a scientific manner. Nevertheless, there is much to measure in an EEG, and what would take the PhD student weeks to read will take a computer microseconds.

A QEEG is simply an EEG attached to a computer that contains appropriate software. A QEEG will immediately demonstrate tumors and brain activity or lack of it related to specific stimuli that are simply not possible to detect on a non-computer-driven EEG. Using QEEG technology operated by an expert physician, we have been able to demonstrate not only lack of normal activity in ME patients but migration of the normal activity centers from injured areas to different parts of the brain. We have also been able to demonstrate that there is considerable interference between the damaged center and the new center. The patient can dampen this interference when not fatigued, but as the stress continues, the interference-dampening capability of the brain fails and the patient goes into a memory and CNS dysfunction situation. Research would be beneficial in this area.

### **FUNDAMENTAL ADVICE**

The following guidelines are useful for all clinicians:

1. When a patient presents with fatigue with no obvious cause, the physician is obliged to search for an occult malignancy, cardiac disease, other organ disease, *or* chronic infection.
2. When a patient presents with changes in mentation, the physician should think in terms of atherosclerotic disease, other arterial injuries, or changes involving the brain. Some of these are easily and inexpensively measured with a Doppler exam.
3. Common things are common. First check out common illnesses that can cause brain dysfunction and fatigue.
4. Never trust your instincts in making a diagnosis. Bizarre behavior does not necessarily mean the patient needs psychiatric treatment, nor does totally normal behavior mean the patient is free from significant injury or illness.
5. If you cannot measure and confirm the dysfunction with scientific or physical tests, you cannot be certain that your diagnosis is correct.

6. Listen to and watch the patient carefully, and take a detailed history. Trust a patient's complaints, but do not trust a patient's self-diagnosis; patients are often wrong or caught up in the latest fad diagnosis. You spent years studying medicine to learn how to make the correct diagnosis, and on the basis of that diagnosis, you may be able to help the patient.
7. Once you have made a diagnosis or have found an anomaly to explain an illness, remember to complete your investigation – several illnesses or medical anomalies may be contributing to the ill health of a single patient. The injury that you find may be part of a larger spectrum of illnesses, some of it treatable.
8. Patients who arrive at the office of a new physician and who have been completely investigated by many excellent physicians are sometimes dismissed as psychiatric or faking. It is in these patients that I find all of the pathology, and some of it is obvious. Rarely do physicians do more than a routine series of tests. The belief that CFS is a psychological illness is the error of our time.
9. If you discover any significant but modest cardiac valve or other cardiac disease on first examination, repeat the Doppler or any essential test in 6 months if the patient develops shortness of breath, otherwise yearly, as this may represent a progressive injury.

If you fail to find any cause of disease, do not assume that the patient has a psychiatric disease or a school or work avoidance. Sometimes either your knowledge or the necessary technology has not been in place to make the diagnosis. Sometimes the patient's symptoms preclude easy recognition of the illness at that date.

## **CASE STUDIES**

### **Case 1**

A new patient, a teacher, came in carrying reams of computer-driven notes. He was 52 years old and had been ill for 18 months. I started by simply asking him his name; a two-hour tirade followed. I did not attempt to stop him although his words were quite irrational. He berated the more than 10 physicians and 4 hospitals he had attended during the previous 18 months. He stated that they had sometimes asked him to leave after a few minutes without so much as examining him. He told me, "They had the nerve to infer that I was a psychiatric patient." He had lost his job as a teacher due to his illness, and these physicians were not willing to help him obtain his disability payments. He said he slept all the time. He said he was still tired after sleeping. He said that he had lost his memory and couldn't teach. He said that he had not received a disability insurance check for over a year. Yet it was apparent to me, and probably to his other physicians, that this patient had a mental illness. His physicians had referred him to psychiatrists who diagnosed a psychosis and placed him on antipsychotic medication. He reacted badly to these medications. He insisted they were wrong; he had diagnosed himself as having chronic fatigue syndrome. He conformed to the CFS definition. He did not complain of his severe obesity. He did not complain of his strong odor, but possibly the smell and the unstoppable irrational babble explained why some of his physicians had asked him to leave their office. The patient was obviously psychotic.

Yet his presumptive and actual diagnosis that was later confirmed was fairly easy to make. During the 2 hours in my office in which I simply sat back and let him talk, hoping he would slow down, he excused himself to urinate 4 or 5 times. Although I did nothing other than to listen to him, he was very happy when he left because I had not only listened but also asked him to come back. As he left, I gave him a requisition for a fasting and 3-hour blood sugar and a few other simple tests.

In four days when he returned, I was able to tell him that he was severely diabetic and that he had an extreme hyperlipidemia. I referred him to the diabetic clinic the next day, where treatment was started immediately. In the two weeks that followed, I was able to demonstrate that he had had a recent myocardial infarct. Within two weeks of the start of his treatment for diabetes, his psychosis had totally disappeared; he talked rationally in a perfectly normal manner; and I was able to take a reasonable history. He was placed in the hands of cardiologists, dieticians, and exercise physiologists. A letter of the findings was sent to his insurer and within 30 days he had received his back disability benefits from the previous year.

The physicians who had seen this patient were undoubtedly competent professionals. They had trusted their instincts and they had made a correct diagnosis. He did have a psychosis, but they did not go far enough to diagnose a relatively easily treatable diabetic encephalopathy. Yet had I been satisfied with the diagnosis of diabetes and diabetic encephalopathy, I would have missed the hypertension, the severe hyperlipidemia, and the myocardial infarct. This example shows why all patients who present with a self-diagnosis of ME or CFS, or a physician referral of ME/CFS, should be given a complete and structured history, as well as a physical and technological examination. Unusual behavior does not always indicate primary psychiatric disease. Often patients have multiple disease problems to explain their illness.

## **Case 2**

This patient phoned me from the United States to ask for an appointment. The young man had visited two major U.S. clinics and had been seen by over 20 physicians in the United States and Great Britain. They had diagnosed him as either having CFS or psychiatric problems. He was a brilliant professional with an extremely high salary who simply wished to get back to the work and life he loved. His story is typical of many patients I have seen. He had been ill with a significant upper respiratory tract infection (URTI) including a severe sore throat. For some unknown reason, his physician decided to give him a combined hepatitis B and A immunization at this time. Within a week after the injection, he was severely ill with intellectual and fatigue dysfunction. He soldiered on for several months mainly through the courtesy of his associates and then finally had to stop. One of his insurance companies refused to pay him. Despite seeing many physicians and going to two of the most important medical clinics in the United States, he was no further along. He brought all of the tests performed on him over the previous two years. It proved to have been a very incomplete investigation, but there were clues. There was a minor TSH discrepancy on one of his tests. On physical exam, there was not much in his thyroid but it was a bit irregular. I ordered antithyroid antibodies that came back incredibly elevated, and the initial ultrasound came back as a nodular thyroid. A thyroid uptake scan came back with a diagnosis of Graves' disease, but this did not fit what appeared to be a Hashimoto's thyroiditis. I referred him to an endocrinologist in his hometown and asked for a biopsy. It came back as

malignant plus Hashimoto's thyroiditis. The thyroid was removed, and he was placed on treatment for metastasis as a precaution.

However, his neuro-SPECT demonstrated a significant vasculitis pattern. What probably happened is that the hepatitis B portion of the immunization paralyzed his normal immune response to the ongoing infection. The existing presumed viral infection then became chronic. I have seen this scenario in many cases of post-hepatitis B immunization injury. The companies producing hepatitis B immunization serum now clearly state in their brochures not to immunize when the patient is ill. When these immunizations first came out, however, they were touted as being the safest immunization ever invented and the suggestion was that they could be given without any negative consequence. Immunizations are powerful tools and should not be used in a patient with an acute ongoing infectious illness. This patient has other injuries that I will not go into, but he has classical ME with the abnormal vasculitis pattern scan. His ME illness is still active, but hopefully will settle down.

### **Case 3**

This patient also called me from the United States. She had been seen and diagnosed as CFS by several clinics and ME/CFS physicians. It seemed foolish for her to waste her time and money. She had significant brain dysfunction and overwhelming fatigue. She had CFS. Her initial investigation took the morning, and I was able to obtain a carotid and transcranial Doppler that afternoon. The exam revealed severe hyperlipidemia and an 80% obstruction of both internal carotids and a complete obstruction of the basilar artery feeding the brain. Her cause of CFS was obvious, but experienced physicians investigating ME/CFS and other neurologists and internists in the United States had missed it. The obstruction in one of the arteries was removed and she improved.

### **Case 4 Group**

This Canadian government employee fell ill at a party, along with several other family members. She had typical acute onset ME including significant CNS dysfunction and rapid exhaustion with physical or intellectual stressors. Her twin daughters also fell ill and had to stop school. A teenage neighbor across the street who was not at the party fell ill the same week; all had the same symptom picture. The next-door neighbor developed leukemia and the neighbor three doors down was diagnosed with Crohn's disease all in the same two weeks. Was it coincidence? Possibly. The girl across the street was ill for 6 months with severe ME/CFS and then recovered totally and not only went back to her university but got top marks in her class.

One of the identical twins recovered and returned to university classes with minor ongoing problems. The other identical twin attempted to return to school but failed miserably. Five years later, the mother and the one twin are still ill. The SPECT brain scans are typical of ME. Why did one twin recover? With PCR (polymerase chain reaction), we were able to find that the mother and the one twin still ill had had a persisting and consistent novel enterovirus for over three years. The twin who recovered had no enterovirus and her immune system had gotten rid of this infection. The ill mother and daughter both have persisting antibodies to their mitochondria.

Another group also in Ottawa fell ill the same week, again at a party; all were family members. One had the same persisting enterovirus that we had followed for three years; the others we were not able to test because government cutbacks had closed our facility. The one woman with the persisting virus was a physical education instructor and government employee and was now suffering from chronic severe CNS problems and rapid exhaustion. A vasculitis SPECT brain pattern has persisted since she was first ill. She had severe dysautonomia and peripheral nerve injuries.

Interesting enough, her uncle, who fell ill at the same party, had CNS problems and profound exhaustion only after playing hockey, a very active sport. He developed rapidly advancing coronary valve injury and this valve had to be replaced. He has been advised to cease playing hockey and has done so; he is now active in golf without any further problems.

Another family member at the same party developed acute psychotic disease and recovered. The enterovirus finding is interesting. We have never recovered this virus in a gradual onset CFS patient. We have never found it in any normal controls except for two individuals who had both received massive blood transfusions and had heart disease. We have found this virus in only about 10% of acute onset patients and have not been able to recover it in patients after 3 years of illness. It is hard not to believe that some ME is not viral related.

## CONCLUSION

Thirty years ago when a patient presented to a hospital clinic with unexplained fatigue, any medical school physician would have told the students to search for an occult malignancy, cardiac or other organ disease, or chronic infection. The concept that there is an entity called chronic fatigue syndrome has totally altered that essential medical guideline. Patients are now being diagnosed with CFS as though it were a disease. It is not. It is a patchwork of symptoms that could mean anything. The original concepts of searching for occult disease are relevant to patients presenting today with CFS, ME, and other fatiguing illnesses. Furthermore, because you do not find pathology does not mean there is none. From 1985 until 1988, I investigated ME/CFS patients in a manner that I thought was exhaustive. I found disease then in only about 10% to 20% of patients. Were the remaining 80% to 90% suffering from somatization, psychiatric disease, or simply faking? No, the error of analysis was in my ability. After I met and received training from specialists including Dr. Charles Poser, a neurologist at Harvard, Dr. John Richardson in the United Kingdom, Dr. Jay Goldstein in Beverly Hills, and Dr. Ishmael Mena, at the University of California-Los Angeles, my ability to diagnose a ME/CFS patient's disability rose 50% to 80%. Today, I usually find the underlying measurable cause of disease in 70% to 80% of the patients that I investigate. Are the remaining 20% suffering from somatization or psychiatric disease? I don't think so. I think I am simply missing the underlying diagnosis.

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FOR FURTHER INFORMATION:

For those who wish to obtain more information on ME/CFS, One Click suggests that you order a copy of ***'The Clinical and Scientific Basis of Myalgic Encephalomyelitis / Chronic Fatigue Syndrome'***, edited by Byron Hyde, MD and available from The Nightingale Research Foundation here: <http://www.nightingale.ca/>

Eighty of the world's leading M.E. / CFS authorities have contributed their knowledge to produce a 725-page encyclopaedia on the disease process that may be one of the biggest single causes of chronic illness in the world today. Known in the United States as Chronic Fatigue Syndrome and in Great Britain both as Myalgic Encephalomyelitis and Post-Viral Fatigue Syndrome, M.E./CFS has provoked a chronic disabling illness in an estimated 1,000,000 persons in North America and Europe.

This book provides, in one superb 75-chapter source, an up-to-date, comprehensive account of current knowledge concerning the history, epidemiology, children with M.E., investigation, virology, immunology, muscle pathology, host response, food intolerance, brain mapping, neurophysiology, neuropsychology, psychiatry, sleep dysfunction, fibromyalgia syndrome, treatment and management.

This is an essential reference book for medical, government and public library reference rooms. This text is a unique vehicle for researchers, physicians and other health education and government officials, and is easily understandable by the general public interested in M.E./CFS.

All funds from this text will be used both to promote research and to assist in greater understanding of M.E./CFS, and a charitable donation tax receipt will accompany the book.

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