



# **The Nightingale Definition of Myalgic Encephalomyelitis (M.E.)**

## **Abstract**

M.E. is a clearly defined disease process. CFS by definition has always been a syndrome.

It essential to define clearly Myalgic Encephalomyelitis. That is what the Nightingale definition of M.E. sets out to do. The definition is based upon two criteria: the excellent scientific work of respected physicians and scientists who investigated the various M.E. epidemics, and our modern scientific testing techniques and the knowledge resulting from examining thousands of M.E. patients using these techniques.

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Published by:  
The Nightingale Research Foundation  
Ottawa, Canada  
<http://www.nightingale.ca>

Version: 29-01-07

## *Dedication*

The following definition of Myalgic Encephalomyelitis (M.E.) was prepared as a result of an invitation to attend two meetings at the British House of Commons with the Honourable Dr. Ian Gibson, Member of Parliament for Norwich North. The first meeting was with Dr. Gibson and his parliamentary assistant, Huyen Le, on 27 October 2005.

The second meeting was with The United Kingdom Parliament Group on Scientific Research into Myalgic Encephalomyelitis (M.E.), composed of Members of the House of Commons and House of Lords. It was held at Portcullis House on 10 May 2006. The committee members included:

### **The House of Commons Committee on M.E.**

- Dr. Ian Gibson (Labour MP for Norwich North)
- Dr. Richard Taylor (Independent MP for Wyre Forest)
- Rt Honourable Michael Meacher (Labour MP for Oldham West and Royton)
- David Taylor (Labour MP for North West Leicestershire)
- Dr. Des Turner (Labour MP for Brighton Hemptown)

### **The House of Lords Committee on M.E.**

- Lord Leslie Arnold Turnberg (Labour) Royal College of Physicians
- Baroness Julia Frances Cumberlege (Conservative)
- The Countess of Mar

The Chairman of the joint committee, Dr. Ian Gibson, asked me to prepare a report that might assist the committee in its further deliberations. Here is what I recommended.

### **The Report**

It became obvious to me that too much importance is being placed upon the definitions of Chronic Fatigue Syndrome, and not enough upon the actual disease, Myalgic Encephalomyelitis. These two illness spectrums are not the same and should not be considered to be the same. Nor is there any doubt in my mind that the various definitions of CFS actively impede physicians' ability to make a rapid diagnosis and a scientific confirmation of the illness, thus preventing a possible immediate treatment of some of these significantly disabled M.E. patients.

The following definition and discussion, although completed after the tabling of the parliamentary report, has been nevertheless respectfully submitted to the Honourable Dr. Ian Gibson M.P. and his committee members of the House of Lords and Commons.

I hope that this definition will be helpful to Dr. Gibson and his committee in their deliberations and will give comfort to M.E. patients everywhere. It is a definition that allows physicians to diagnose and treat successfully some of these patients immediately. Many underlying pathologies of M.E. are already known, particularly the primary physiological vascular dysfunctions, but effective treatment is simply not available. This definition also suggests the direction that future research into these vascular pathophysiology might take.

# The Nightingale Definition of Myalgic Encephalomyelitis (M.E.)

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## Preface

Since the Nightingale Research Foundation's publication in 1992 of the textbook, *The Clinical and Scientific Basis of Myalgic Encephalomyelitis / Chronic Fatigue Syndrome* (Hyde, B, 1992), there has been a tendency by some individuals and organizations to assume that M.E. and CFS are the same illness. Over the course of two International Association of Chronic Fatigue Syndrome (IACFS, formerly the American Association of CFS) conferences, there have been suggestions that the name CFS be changed to M.E., while retaining the CFS definitions (Holmes, G.P., Sharpe, M.C., Fukuda, K) as a basis for such change. This does not seem to me to be a useful initiative: it would simply add credence to the mistaken assumption that M.E. and CFS represent the same disease processes. They do not.

### **M.E. is a clearly defined disease process. CFS by definition has always been a syndrome.**

At one of the meetings held to determine the 1994 U.S. Center for Disease Control (CDC) definition of CFS, in response to my question from the floor, Dr. Keiji Fukuda stated that numerous M.E. epidemics - she cited the Los Angeles County Hospital epidemic of 1934 (Gilliam, A.G.), the Akureyri outbreak of 1947-48 (Sigurdsson, B.) and the 1955-58 Royal Free Hospitals epidemics (Ramsay, A.M.) were definitely not CFS epidemics. Dr. Fukuda was correct.

### **The Psychiatric Label:**

Unfortunately many physicians and some senior persons in governments, including Great Britain, Norway and to a lesser degree the USA and Canada treat CFS as a psychiatric illness. This view has

been arrived at by some physicians' interpretations of the CFS definitions from the Center of Disease Control (CDC). Indeed, despite clear signals in the 1994 CDC definition that CFS is not a psychiatric disease (Fukuda, K.), each of the CDC definitions and their addenda referring to CFS remain open to interpretation as a psychiatric rather than a physical illness. This is not a view to which I subscribe. It is the CFS definitions themselves that give rise to this inaccuracy. Consider the following:

- a) What other physical disease definitions essentially state that if you discover the patient has any physical injury or disease, then the patient does not have the illness CFS? In other words if you have CFS then it does not result in or cause any major illness. What else could CFS then be but any number of various psychiatric, social, hysterical or mendacious phenomena?
- b) The various CDC administrations dealing with the subject have clearly stated that CFS is a physical, not a psychiatric disease. However, is there any other definition of any physical disease that is not provable by scientific and clinical tests? Only psychiatric diseases are not clearly verifiable by physical and technological tests.
- c) What other physical disease definition requires a 6-month waiting period before the illness can be diagnosed? Any physician knows that to treat a disease adequately you have to be able to define the disease at its onset and treat it immediately in order to prevent chronic complications from arising. To my knowledge, in the entire history of medicine, there are simply no other disease definitions that have

ever been assembled with a structure similar to the CFS definitions.

- d) If you are still not convinced, check the Internet for the definition of: *DSMIII Somatization Disorder*. (DSM) You will find that there is little substantial difference to distinguish the DSMIII definition from the 1988 and 1994 CDC definitions of CFS. It is difficult to believe that the CDC medical bureaucracy is not aware of this similarity. It is thus understandable why the insurance industry, as well as some psychiatrists and physicians, have simply concluded that CFS, if it exists, is a somatization disorder.

I believe it essential to define clearly Myalgic Encephalomyelitis, returning the definition to its clinical and historic roots and complementing this information with the certitude of modern scientific testing. That is what the Nightingale definition of M.E. sets out to do. But let me first ask you a very important question.

### **What is the purpose of any medical definition?**

What is the purpose of any disease definition if it is not to allow the physician to rapidly and accurately diagnose a specific illness in order to attempt to effectively treat the patient before the illness becomes chronic or to call in the appropriate specialists? Our definition solves this problem.

What then is the purpose of any disease definition, once the disease has become chronic, if it is not:  
(a) to elicit clues for the immediate effective treatment of at least some of the patients, (b) to

separate out illnesses with a similar symptom pictures in order to effectively treat them and finally (c) to direct research into reversing pathophysiological injuries that can be defined in terms of modern testing but for which, there is no effective treatment. Our definition solves this problem.

There is a third purpose for any disease definition. That is to clearly define the spectrum and limits of the disease so that various physicians and researchers can clearly understand that they are talking about the same illness spectrum and so launch research into what will become an effective treatment. Our definition gives a clear baseline for investigation.

The Nightingale definition is based upon the following two criteria:

- (a) The excellent scientific and clinical work of respected physicians and scientists who investigated the various M.E. epidemics.
- (b) The results of modern scientific testing techniques and the knowledge accruing from examining thousands of M.E. patients using these and more historical techniques.

The proposed M.E. definition is designed to improve early diagnosis and treatment for the tens of thousands of patients stricken with M.E.

It is not a new definition of CFS nor should it be conceived as a rewording of any previous CFS definition. What follows is the primary M.E. definition for adults.

## The Nightingale Definition of Myalgic Encephalomyelitis (M.E.)

**Primary M.E. is an acute onset biphasic epidemic or endemic (sporadic) infectious disease process, where there is always a measurable and persistent diffuse vascular injury of the CNS in both the acute and chronic phases. Primary M.E. is associated with immune and other pathologies.**

Primary M.E. is a chronic disabling, acute onset biphasic epidemic or endemic (biphasic) infectious disease process affecting both children and adults. There are both central and peripheral aspects to this illness.

- A)** The Central Nervous System (CNS) symptoms, as well as the clinical and technological abnormalities, are caused by a diffuse and measurable injury to the vascular system of the Central Nervous System. These changes in the organization of the CNS are caused by a combined infectious and immunological injury and their resulting effect on CNS metabolism and control mechanisms. Much of the variability observed in an M.E. patient's illness is due to the degree and extent of the CNS injury and the ability of the patient to recover from these injuries.
- B)** A significant number of the initial and long-term peripheral or body symptoms, as well as clinical and technological body abnormalities in the M.E. patient, are caused by variable changes in the peripheral and CNS vascular system. The vascular system is perhaps the largest of the body's organs and both its normal and patho-physiological functions are in direct relationship to CNS and peripheral vascular health or injury, to CNS control mechanisms and to the difficulty of the peripheral vascular system and organs to respond to CNS neuro-endocrine and other chemical and neurological stimuli in a predictable homeostatic fashion.
- C)** When pain syndromes associated with M.E. occur, they are due to a combined injury of (i) the posterior spinal cord and / or posterior root ganglia and appendages, (ii) patho-physiological peripheral vascular changes, and (iii) CNS pain reception homeostasis mechanisms.

Depending upon the degree and extent of the ongoing CNS and peripheral vascular injuries, these patho-physiological changes in turn may give rise to both transient and in many cases permanent systemic organ changes in the patient.

As with any illness, the diagnostic criteria of M.E. are divided into two sections:

- (a) The clinical features and history of the ill patient that alert the physician to the initial diagnosis, and
- (b) The technological examinations that confirm to the physician proof of his diagnosis.

### Clinical Features

The clinical features of Myalgic Encephalomyelitis are consistent with the following characteristics that can easily be documented by the physician.

- 1. M.E. is an acute onset biphasic epidemic or endemic (sporadic) infectious disease process:** Both Epidemic and Non-Epidemic cases are often preceded by a series of repeated minor infections in a previously well patient that would suggest either a vulnerable immune system, or an immune system subject to overwhelming stressors such as: **(a)** repetitive contact with a large number of infectious persons, **(b)** unusually long hours of exhausting physical and / or intellectual work, **(c)** physical traumas, **(d)** immediate past immunizations, particularly if given when the patient has concurrent allergic or autoimmune or infectious disease or if the patient is leaving for a third world country within three weeks of receiving the immunization, **(e)** epidemic disease cases whose onset and periodicity appear to occur cyclically in a susceptible population, **(f)** the effect of travel, as in exposure to a new subset of virulent infections, or **(g)** the effects of starvation diets. (It should be noted that subsets c, d, e, f and g are all stressors associated with decreased immune adaptability **plus** an associated infection with an appropriate neurovascular infectious virus or other infectious agent. This may be due either to an immediate preexisting infectious disease or to a closely following infection, either of which may or may not be recognized.)

2. **Primary Infection Phase:** The first phase is an epidemic or endemic (sporadic) infectious disease generally with an incubation period of 4 to 7 days; in most, but not all cases, an infection or infectious process is evident. (See *Clinical and Scientific Basis of M.E./CFS, Chapter 13, pps. 124-126*)
3. **Secondary Chronic Phase:** The second and chronic phase follows closely on the first phase, usually within two to seven days; it is characterized by a measurable diffuse change in the function of the Central Nervous System. This second phase is the persisting disease that most characterizes M.E.
4. **The Presence or Absence of Various Pain Syndromes is highly variable:** The pain syndromes associated with the acute and chronic phases of M.E. may be described as **Early** and **Late** findings. **Early Findings:** (a) severe headaches of a type never previously experienced; (b) these are often associated with neck rigidity and occipital pain; (c) retro-orbital eye pain; (d) migratory muscle and arthralgia pain; (e) cutaneous hypersensitivity. **Late Findings:** Any of the early findings plus (f) fibromyalgia-like pain syndromes. This is only a partial list of the multiple pain syndromes. Many of the pain features tend to decrease over time but can be activated or increased by a wide range of external & chemical stressors. (See *Clinical and Scientific Basis of M.E./CFS, Chapter 5, pps. 58-62*)

### Testable & Non-testable Criteria

The technological tests listed below can be used to (a) confirm the clinical diagnosis of Myalgic Encephalomyelitis and (b) to some degree gauge its severity and probability of persistence. The second and chronic phase that clearly defines M.E. is characterized by various measurable and clinical dysfunctions of the cortical and/or sub-cortical brain structures.

5. **Diffuse Brain Injury Observed on Brain SPECT:** If the patient's illness is not measurable using a dedicated brain SPECT scan such as a Picker 3000 or equivalent, then the patient does not have M.E. For legal purposes these changes may be confirmed by PET brain scans with appropriate software and /or QEEG. These changes can be roughly characterized as to severity and probable chronicity using the

following two scales: **A)** Extent of injury and **B)** degree of injury of CNS vascular function.

### Extent of Injury

**Type 1:** One side of the cortex is involved. Those patients labeled as 1A have the best chance of recovery.

**Type 2:** Both sides of the cortex are involved. These patients have the least chance of spontaneous recovery.

**Type 3:** Both sides of the cortex, and either one or all of the following: posterior chamber organs, (the pons and cerebellum), limbic system, the subcortical and brainstem structures are involved. Type 3B are the most severely affected patients and the most likely to be progressive or demonstrate little or no improvement with time.

### Degree of injury

**Type A:** Anatomical integrity is largely maintained in the Brain SPECT scan.

**Type B:** Anatomical integrity is not visible in the CNS SPECT scan. Type 3B are some of the most severely and chronically injured patients.

6. **Testable Neuropsychological Changes:** There are neuropsychological changes that are measurable and demonstrate short-term memory loss, cognitive dysfunctions, increased irritability, confusion, and perceptual difficulties. There is usually rapid decrease in these functions after any physical or mental activity. Neuropsychological changes must be measured in relation to estimates of prior achievement. This feature may improve over a period of years in patients with adequate financial and social support and can be made worse by chronic stressors.

The neurophysiological changes are those observed by a qualified Neuropsychologist with experience in examining this type of disease spectrum. Some of the deficits that a Neuropsychologist should consider examining include: (a) word finding problems, (b) Subtle problems with receptive and expressive aphasia,

(c) Decreased concentration, (d) Distractibility and the decreased ability to process multiple factors simultaneously, (e) Dyscalculia, (f) Decreased fine and gross motor problems, (g) Dysfunction of spatial perception, (h) Abstract reasoning, (i) Compromised visual discrimination, (j) Sequencing problems. In Cochran's Q Neuropsychological tests there is an increased observation of significant problems in both immediate and delayed verbal recall. In Dr Sheila Bastien's investigations, over 50% of M.E. patients have delayed visual recall, TAP dominance, TPT N-Dominance and 40% or more have abnormalities of Immediate visual recall, Tap N-Dom, Grip N Dominance, & grip dominance problems (*Bastien, Sheila. The Clinical and Scientific Basis of M.E. / CFS. Chapter 51, pps. 453-460*)

7. **Testable Major Sleep Dysfunction:** This can include all forms of sleep dysfunctions. All or any of the following may be present: (a) impaired sleep efficiency, (b) significant fragmented sleep architecture, (c) movement arousals, particularly if there is an associated pain syndrome, (d) absence or significant decrease of type 3 and 4 sleep, (e) abnormal REM sleep pattern (f) changes in daytime alertness and (g) sleep reversals.
8. **Testable Muscle Dysfunction:** This feature may be due to vascular dysfunction or peripheral nervous or spinal dysfunction and includes both pain and rapid loss of strength of muscle function after moderate physical or mental activity. This feature tends to improve over a period of years but many patients frequently remain permanently vulnerable to new disease episodes. Few centres are equipped or funded to make these examinations. Unfortunately only a few major medical centres are equipped to study this type of dysfunction.
9. **Testable Vascular & Cardiac Dysfunction:** This is the most obvious set of dysfunctions when looked for and is probably the cause behind a significant number of the above complaints. All moderate to severe M.E. patients have one or more and at times multiple of the following vascular dysfunctions. As noted, the primary vascular change is seen in abnormal SPECT brain scans and clinically most evident in patients with:

**a) POTS:** severe postural orthostatic tachycardia syndrome. **Note:** This group can be confused with diabetes insipidus due to the fact that they may have polydipsia from their attempt to increase their circulating blood volume by consuming large amounts of fluids. This group can be verified by the absence of pituitary adenoma or pathology and the fact that they can sleep through the night without waking to drink fluids (Streeten, David.) Despite the great steps forward in the understanding of this relatively common pathophysiology seen routinely in M.E. patients, a pathology which is really related to either an autonomic injury to the CNS, injury to the vascular receptors or both, very little of the present treatment protocol is of much use. The situation is so bad that few major centres have any well-funded expertise in either autonomic or vascular receptor injury. Many of the M.E. patients that are dismissed by physicians as suffering from lack of activity have significant proprioceptive injuries in these areas. Nor can we always rely on the few autonomic laboratories and their tilt table testing abilities. Many of the tilt table examination reports return as normal, many as grossly abnormal. Yet all the physician has to do is have each M.E. patient stand for 8-12 minutes to realize that a large number of these normal tilt table patients simply cannot maintain a normal blood pressure and normal heart rate. Compare this to non-M.E. patients and one immediately can tell the difference. A large number of M.E. patients have significant autonomic difficulties.

**b) Cardiac Irregularity:** on minor positional changes or after minor physical activity, including inability of the heart to increase or decrease in speed and pump volume in response to increase or decrease in physical activity. (Hyde, B., Chapter on Cardiac Aspects): (Montague, T.,) Cardiac irregularity is closely related to the above discussion. In many M.E. patients there is an unusual daytime tachycardia, particularly since these patients are often very sedentary. In doing a 24-hour Holter monitor this may be missed since the 24 hour average is usually given. One should always ask for wake time and sleep time heart rates.

**c) Raynaud's Phenomenon:** vasoconstriction of small arteries or arterioles of extremities, with change in colour of the skin, pallor and cyanosis. It is associated with coldness and pain of

extremities. This is in part, the cause for temperature and pain dysfunctions seen in M.E. This phenomenon is found in many other conditions than M.E. Some of the associations are post-traumatic, neurogenic conditions, occlusive arterial diseases, toxic chemical associations and a wide range of rheumatoid conditions. Many of these conditions have associations with M.E. (See Magallini, S. for more detail.)

**d) Circulating Blood Volume Decrease:** This is a nuclear medicine test in which the circulating red blood cell levels in some M.E. patients can fall to below 50%, preventing adequate oxygenation to the brain, gut and muscles. These patients do not generally have anemia and are not blood deficient. This is undoubtedly a subcortical dysregulation. It is associated with serum and total blood volume measurements. This is a concept that many physicians have difficulty understanding. I have heard physicians repeatedly tell the patient they are not anemic and therefore dismiss this important finding. **Note:** So where does the blood go? Body servomechanisms are genetically designed so that blood flow and oxygen to the heart are always protected. Thus, when the body of the M.E. patient is stressed, the blood flow to organs not necessary for short-term survival, such as the brain, the gut and skeletal muscles, can be temporarily decreased. This of course gives rise to many of the M.E. symptoms.

**e) Bowel Dysfunction:** vascular dysfunction may be the most significant causal basis of the multiple bowel dysfunctions occurring in M.E. (See d. above.)

**f) Ehlers-Danlos Syndromes Group:** This is a group of illnesses with a genetic predisposition to M.E. or M.E.- like illness. In fact it probably represents a spectrum of illnesses that start with (i) hyper-reflexia syndrome, moving through any of the (ii) various Ehlers-Danlos Syndromes and climaxing in (iii) Marfan Syndrome where there tends to be early death if the aortic and cardiac changes are not repaired. Ehlers-Danlos syndromes can go undetected until what appears to be a switch is turned on, usually in late teens to early thirties. The “switch” may be viral or possibly age or hormonal related. Raynaud’s phenomenon is usually associated. **Diagnosis:** briefly, patients over the age of 16 who can (i) touch their nose with their tongue, (ii) touch their

forearm with the thumb of the same extremity (joint laxity), (iii) touch the floor readily with the full palm should be considered suspect for further examination. There are several fasciation variations of Ehlers-Danlos. They are generally considered to be a group of genetic illnesses but in my examination of M.E. patients most often are not manifested until well past puberty and in adulthood. Additional generalized features of this spectrum of illnesses include (v) India rubber or hyperelastic skin, (vi) easy bruisability (vascular fragility), (vii) Arachnodactyly (long spiderlike fingers). Many of the patients with a more severe form tend to be tall, slender with a dolichocephalic skull, high palate and long narrow feet with hammertoes verging on Marfan syndrome. (See Magalini, S. I., Magalini S. C. for both E-D Syndrome and Marfan 1 and Marfanoid hypermobility.)

**g) Persantine Effect in M.E. Patients:** Persantine is a chemical manufactured by Boehringer Ingelheim. It is employed to perform chemical cardiac stress testing when a patient cannot exercise sufficiently to stress the heart. It is a particularly safe medication but when employed with many M.E. patients it can cause severe muscle pain over the extremities and entire musculature. Normally this can be reversed by injection of an antidote but this does not always work rapidly in M.E. patients. Severe pain and fatigue can be intolerable and persist for minutes to days in some M.E. patients following Persantine use. Persantine works by dilating both peripheral and cardiac blood vessels and causing the heart rate to increase as in a POTS patient. Obviously one major pain and fatigue factor in M.E. patients is caused by abnormal dilatation of peripheral blood vessels. The resulting pain may be related to reflex vasospasm as in severe Raynaud’s phenomenon that I note elsewhere is one of the causes of M.E. pain. To my knowledge, no testing of M.E. patients with Persantine has ever been published by Boehringer Ingelheim or others. It is one of the reasons I believe that pain syndromes in M.E. patients are due to a pathological vascular physiology.

**h) M.E. Associated Clotting Defects:** M.E. represents both a vasculitis and a central and peripheral change in vascular physiology. All such vascular illnesses should be potentially treatable. We do not yet know how to adequately treat the (i)

genetic forms of vasculitis & vascular pathophysiology mentioned here, nor (ii) the probable viral triggered genetic vascular pathologies also mentioned. Nor do we know how to treat those (iii) centrally caused injuries causing the circulating blood volume defects that are demonstrated when we do the “nuclear medicine circulating blood volume tests. It is important to do this test on all patients. POTS is poorly treatable and more often success in treatment presently escapes physicians’ ability. Eventually, I have no doubt that these will be treatable causes of M.E. type disease. However there is a significant group of M.E. patients who are ill due to a treatable form of vasculitis and can be treated if the physician takes the time to diagnose the subgroup. These patients are the clotting defect patients. Some of these clotting defects are genetic and some appear to be genetic with an age or viral switching mechanism, as I have mentioned elsewhere with Ehlers Danlos Syndromes; although they may develop in childhood, they are more frequently noted well after puberty and before the age of 40. Many of these patients can be diagnosed by the following tests: (1) Serum viscosity test, (2) Antiphospholipid Ab., (3) Protein C defects, (4) Protein S defects, (5) Factor V Leiden defect, to name the most common that we have uncovered. However, there are others for which we also test. These conditions are all potentially treatable and when treated adequately may allow the patient to return to school or work. Although any physician can order these tests, a haematologist should review all M.E. patients for these and other possible clotting anomalies. Most clotting defects are treatable and treatment has resulted in recovery in some cases. Remember M.E. is essentially a problem of microcirculation and any improvement in this area can have dramatically positive effects. It is well worthwhile for all physicians reading this definition who have an interest in M.E. to examine the Internet for Hughes Syndrome. Curiously, Hughes Syndrome was first outlined in St. Thomas’ Hospital London, the home of the Nightingale School of Nursing. Hughes Syndrome, a vascular syndrome also called Sticky Blood Syndrome, closely parallels the definition of M.E.

**i) Anti-smooth muscle Antibodies:** This is an antibody to the muscle tissue in the arterial bed. It is elevated in about 5% of M.E. patients but

whether this is different in non-M.E. patients is unknown but unlikely. It rarely is over 1:40.

**j) Cardiac Dysfunction:** There are a large number of cardiac dysfunctions that can regularly appear in an M.E. patient. Certain are obvious and discussed under **Ehlers-Danlos Syndrome** and Marfan syndrome. I also discussed cardiac dysfunction in Chapter 42, *The Clinical and Scientific Basis of M.E./CFS*. Since that chapter was written a large number of other cardiac pathologies and pathophysiology have been noted by various researchers and clinicians, particularly by Dr. Paul Cheney. Without a clear understanding of these significant problem areas **it is simply indefensible and potentially dangerous to place an unsuspecting patient in a graduated exercise program**. This is particularly true if the patient is not being tested in a cardiac unit. Although in our clinic we have performed what we believe to be a complete cardiac assessment on all patients seen, what the Ottawa Cardiac Institute and I believed was a complete assessment may be wanting. Over the next year we will reassess these patients with a more detailed cardiac examination and report on it in these diagnostic criteria.

**10. Testable Endocrine Dysfunction:** These features are common and tend to be of late appearance. They are most obvious in:

**a) Pituitary-Thyroid Axis:** Changes in serum TSH, FT3, FT4, Microsomal Ab., PTH, calcium and phosphorous rarely occur until several years after illness onset. This anomaly can best be followed by serial ultrasounds of the thyroid gland, where a steady shrinking of the thyroid gland may occur in some M.E. patients with or without the development of non-serum positive Hashimoto’s thyroiditis (a seeming contradiction in terms) and a significant increase in thyroid malignancy. In cases of thyroid wasting, serum positive changes tend to occur only after years and often not until the thyroid gland shrinks from the normal 13 to 21 cc. volume in an average adult female and 15-23 cc. volume in male patients to below a volume of 6 cc. (Mayo Clinic averages) (Rumack, Carol). The normal serum analysis of patients for thyroid dysfunction, TSH, FT4, microsomal antibodies etc., the golden rule of most physicians and endocrinologists, is simply not an adequate means of ascertaining thyroid

dysfunction in most M.E. patients. Repeat thyroid ultrasound must be performed for all M.E. patients to observe the presence of dystrophic changes. It is also inadequate simply to accept the radiologist's report of a normal thyroid. The volume of each lobe and its homogeneity must be requested and documented. Radiologists simply report normal thyroids when in effect they are hypo and hypertrophic. Although the Mayo Clinic averages cited above may be criticized they are as good as any in ascertaining normal thyroid size.

**The following changes, while uncommon, may also be related to an M.E. disease process:**

**b) Pituitary-Adrenal Axis Changes:** where changes and findings are infrequent.

**c) Pituitary-Ovarian Axis Changes**

**d) Bladder Dysfunction Changes:** This dysfunction occurs frequently in the early and in chronic disease in some people. In some instances this may be due to a form of diabetes insipidus, in other cases it is related to POTS-type illness where the patient is compensating for the inability to maintain vascular pressure by attempting to increase fluid volume. In other cases this may be due to interstitial cystitis or a form of polio-type-bladder particularly if the cause of the individual disease is an enterovirus. Dr. John Richardson also associated this finding with adrenal dysfunction that he measured.

## Discussion

To various degrees many if not all of the above historic findings have been observed and discussed by Doctors Alexander Gilliam, Bjorn Sigurdsson, Alberto Marinacci, Andrew Lachlan Wallis, A Melvin Ramsay (Elizabeth Dowsett), John Richardson, Elizabeth Bell, Alexis Shelokov, David C Poskanzer, W.H. Lyle, Sir E. Donald Acheson, Louis Leon-Sotomayor, J. Gordon Parish and many others. Some of these features have not been noted previously.

To various degrees the following physicians have also noted many of the above historical and the more recent investigational findings. They include alphabetically, Doctors Peter Behan, David Bell, Dedra Buchwald, Paul Cheney, Jay Goldstein, Seymour Grufferman, Byron Hyde, Anthony L Komaroff, Russell Lane, Ismael Mena, Harvey Moldofsky, James Mowbray, Daniel Peterson, Vance Spence and scores of others. I have examined patients with M.E. since the late 1970s but only in 1985 at the urging of Dr. Charles Poser of Beth Israel Hospital at Harvard and John Richardson in Newcastle-upon-Tyne did I take up the study of these unfortunate patients on a full time basis. The material in this definition is the cumulative result of my listening and interpreting the work of all of the above clinicians and my evaluation of over 3,000 M.E. and CFS patients since 1984. The essential concept of the indepth medical evaluation that is the basis of my work on M.E. and CFS since 1995 was crystallized in my discussions in Seattle Washington

State in 2002 with Dr. Leonard A. Jason, Patricia A. Fennell and Renee R. Taylor. This discussion was set down as *Chapter 3, The Complexities of Diagnosis* in their book, *The Handbook of Chronic Fatigue Syndrome*, 2003, John Wiley and Sons, Hoboken, New Jersey (See Jason, Leonard A.). I would also like to thank Elizabeth Dowsett and Jane Colby whose work with children in the UK as well as their advice has been instrumental in this definition. I must also thank each and every one of the members of John Richardson's Newcastle Research Group who have provided me with so much valuable information over the years and who have all supported my continued investigations of M.E. patients.

**What is new and different about the Nightingale M.E. definition is the following:**

**A. A Testable Definition:** The definition is set out in such a fashion as to enable the physician to make a bedside or office clinical diagnosis and then to scientifically test the hypothesis. This will allow the physician an early diagnostic understanding of this complex illness and a scientific and technological method to investigate and confirm the diagnosis. It is well known by all serious physicians that in order to assist any patient in a partial or full recovery the illness must be (a) prevented from occurring by either immunization or understanding and avoiding the causes, (b) or diagnosed and treated immediately

following onset. The Nightingale Definition assists the physician both in diagnosis and early treatment.

**B. A Vascular Pathophysiology.** The subject of vascular pathology is not new. The fact of the children dying of a Parkinsonian-like vascular injury to the basal ganglia in Iceland during the Akureyri M.E. Epidemic is an obvious indication of the CNS vascular effects in M.E. Vasculitis has been well documented by Dr. E. Ryll in his description of the epidemic in the San Juan Mercy, Sacramento California Hospital in 1975. He described this M.E. epidemic as an epidemic vasculitis.

He was correct. In the late 1980s Drs. Jay Goldstein and Ismael Mena confirmed and proved this initial description by examining the changed brain microcirculation using brain SPECT imaging in M.E. patients. Following my 21 years of examining M.E. and CFS patients and 16 years of subjecting the M.E. and CFS patients to brain imaging techniques suggested by Goldstein and Mena, it has become obvious to me that we are dealing with both a vasculitis and a change in vascular physiology. Numerous other physicians have supported this finding. Dr. David Bell, who rediscovered the work of Dr. David Streeten and his book, *Orthostatic Disorders of the Circulation*, advanced this understanding of M.E. The work of Dr. Vance Spence and his colleagues in Scotland have started to nail this CNS-vascular relationship down even further with a series of major research papers. The recent interpretation of the cause of Multiple Sclerosis (MS), as an injury of the microvasculization causing the injury of the schwann cells that in turn causes the demyelination injuries of MS has been added to that of paralytic poliomyelitis as an essential vascular injury. Paralytic poliomyelitis was thought to be a primary injury to the anterior horn cells of the spinal cord but is now recognized as a vasculitis injuring the circulation to the anterior horn cells. Poliomyelitis is generally a non-progressive, specific site injury, although post-polio syndrome with demonstration of subcortical brain changes has challenged that belief. MS is a recurrent more fulminant physiological vascular injury. M.E. appears to be in this same family of diseases as paralytic polio and MS. M.E. is definitely less fulminant than MS but more generalized. M.E. is less fulminant but more generalized than poliomyelitis. This relationship of M.E.-like illness to poliomyelitis is not new and is of course the reason that Alexander Gilliam, in his analysis of the Los Angeles County General Hospital

M.E. epidemic in 1934, called M.E. atypical poliomyelitis.

**C. The Lack of Mention of Fatigue:** M.E. is not CFS: Fatigue was never a major diagnostic criterion of M.E. Fatigue, loss of stamina, failure to recover rapidly following exposure to normal physical or intellectual stressors occur in most if not all progressive terminal diseases and in a very large number of chronic non-progressive or slowly progressive diseases. Fatigue and loss of stamina are simply indications that there is something wrong. They cannot be seriously measured, are generally subjective and do not assist us with the diagnosis of M.E. or CFS or for that matter any disease process.

**D. Cause:** It is obvious that all cases of epidemic M.E. and all primary M.E. are secondary to infectious / autoimmune phenomena. Many M.E. and M.E.-like patients' illness is complicated by multiple other causes, some of which occur unnoticed prior to the illness and some that occur due to the illness itself. This is why a complete technological investigation has to be made on each chronically ill M.E. or M.E.-like patient. Under epidemic and primary M.E. there is no consensus as to the viral or infectious cause. Much of this lack of consensus may be due in large part to separate acute onset from gradual onset patients in the M.E. and CFS groups of patients. Primary M.E. is always an acute onset illness. Doctors A. Gilliam, A. Melvin Ramsay and Elizabeth Dowsett (who assisted in much of his later work,) John Richardson of Newcastle-upon-Tyne, W.H. Lyle, Elizabeth Bell of Ruckhill Hospital James Mowbray of St Mary's and Peter Behan all believed that the majority of primary M.E. patients fell ill following exposure to an enterovirus. (Poliovirus, ECHO, Coxsackie and the numbered viruses are the significant viruses in this group, but there are other enteroviruses that exist that have been discovered in the past few decades that do not appear in any textbook that I have perused.) I share this belief that enteroviruses are a major cause. Unfortunately, it is very difficult to recover polio and enteroviruses from live patients. Dr. James Mowbray developed a test that demonstrated enterovirus infection in many M.E. patients but I do not believe he qualified his patients by acute or gradual onset type of illness. In my tests in Ruckhill Hospital in viral infection only in acute onset patients and not in any gradual onset patients. Few physicians realize that almost all cases of poliovirus recovered from poliomyelitis victims came from cadavers. At the very least, these enteroviruses must be recovered from

patients during their onset illness and this has rarely been done. An exception is in the case of the Newton-le-Willows Lancashire epidemic where Dr. W. H. Lyle's investigation recovered ECHO enterovirus. Recent publications by Dr. J. R. Kerr have also identified the fact that enteroviruses are one of the most likely causes of M.E. If this belief is correct, many if not most of the M.E. illnesses could be vanquished by simply adding essential enteroviral genetic material from these enteroviruses to complement polio immunization.

**Non-Infectious M.E. Type Disease:** I have not discussed noninfectious M.E.-type disease. Similar M.E. phenomena can occur due to diffuse CNS injuries from toxic chemical injury. I have seen this in police officers who have fallen into toxic chemical ponds in pursuit of those suspected of criminal activity. I have seen it in farmers repeatedly exposed to pesticides and herbicides, in hospital and industrial workers and in military personnel in contact with toxic chemicals, specifically toxic gases. I will discuss these at a later date as Secondary M.E. They do have one thing in common, and that is they also have a diffuse CNS injury as noted on brain SPECT scans. The diagnosis is made by history, as the actual cases are very difficult to diagnose due to the inability to assess brain levels of toxins in a live patient. Often these Secondary M.E. diseases are more severe than the infectious M.E. cases.

**E. Caution:** One should be careful in applying the diagnostic criteria discussed under the Nightingale M.E. Definition without also completing a thorough investigation. M.E., whether we are discussing primary or secondary forms, involves a significant diffuse injury of the Central Nervous System and an associated injury of the Immune System. This always implies the potential for secondary injuries or secondary diseases or pathologies caused by a dysfunctional brain and dysfunctional immune system. When the immune system is injured there is an impairment of the patient's ability to resist the development of malignancy as well as other important organ and systemic injuries.

**F. Thyroid Cancer and Thyroid Atrophy:** Due to funding limitations, we have demonstrated in our work only two characteristics of this corollary injury. The first is the high incidence of thyroid cancer in M.E. patients. In the general public, cancer of the thyroid occurs in 1-15 cases per 100,000. In our studies, in the case of the M.E. patient, thyroid cancer has an

incidence of 6,000 cases per 100,000. For whatever reason, even if our figures represent some type of anomaly, the direction is obvious and suggestive of a major pathological association. We have already mentioned the pervasive vascular injuries. We believe that other pathological associations also occur. Failure to evaluate fully the M.E. patient may result in the physician missing important secondary pathology and possibly giving rise to patient death. **All M.E. patients as well as all chronic illness patients deserve a systematic and total body investigation. No individual should go through life, ill, disabled without knowing why he is ill. Simply offering a label, whether M.E. or CFS, without looking at the pathophysiology that gives rise to these disorders, is both unacceptable and potentially dangerous both for the patient and the patient's physician.** (See "*The Complexities of Diagnosis*" by Byron Hyde, in the *Handbook of Chronic Fatigue Syndrome*, Eds. L. A. Jason, P. A. Fennell and R. R. Taylor. John Riley and Sons Inc. Hoboken N.J., 2003. This chapter is also available on various websites.)

**G. Caution 2:** Insurance companies regularly employ reputedly independent psychologists who demonstrate normal neuropsychological findings. Since the patient's data is unreliable if a test is done too frequently, the use of an insurance psychologist presents a grave problem in that neuropsychological testing by a truly independent Neuropsychologist may be delayed for up to a year before the patient can be properly tested. The conflicting results may tend to confuse any trial judge in a legal case.

**H. Depression, Anti-depressive Medications and M.E.:** M.E. is not depression; M.E. is not hysteria; M.E. is not a conversion disorder nor is it a somatization disorder; M.E. is an acute onset diffuse injury of the brain. Psychiatrists should not ever be placed in charge of diagnosis and treatment of M.E. patients. It is simply not their area of expertise and their meddling has at times caused great harm to M.E. patients. Also, during the 20 years that I have investigated M.E. patients I have yet to see a single case of real M.E. that has responded to psychiatric pharmacological treatment such that the patient has recovered and been able to return to work or school. This topic is a very large subject and demands a separate publication and this is not the place for it. However I would like to note again the vascular and cardiac pathologies that one encounters in M.E. patients and how M.E. patients are often made worse by one antidepressive medication that is considered

benign. One of the most common anti-depressive medications employed by psychiatrists and physicians in general for M.E. patients is an old pharmaceutical, Amitriptyline. Yet this medication may result in a condition referred to as *Torsade de Pointes*, a cardiac irregularity giving rise to resting tachycardia, QT interval prolongation and significant orthostatic hypotension. Since there is already a high frequency of these anomalies in M.E. patients, the use of Amitriptyline may assist sleep to some degree but may also simply worsen existing M.E. symptomology. I will hopefully return to this subject in another publication.

### **I. Graduated Exercise and the Myalgic**

**Encephalomyelitis Patient:** Possibly due to the fact that some Fibromyalgia patients can be improved by a gradual increase in exercise, or possibly due to the so called protestant ethic that all you have to do to get better is to take up your bed and walk, some physicians have extended the concept of passive or forceful increased exercise to Myalgic Encephalomyelitis patients. This is a common and potentially dangerous, even disastrous misconception. Doctors Jay Goldstein and Ismael Mena, using Zenon SPECT brain scans, demonstrated that the physiological brain function of an M.E. patient rapidly deteriorates after exercise. They also demonstrated that this physiological dysfunction could persist for several days following any of several stressors. The physiological dysfunction occurs whether the activity (or stressor) is physical, intellectual, sensory or emotional. There are several problems with this finding. (1) The first is technological: Zenon is difficult to obtain and few nuclear medicine centres use Zenon. Nor is Zenon a dangerous substance, it is simply not used due to cost cutting. (2) Once the patient reaches a plateau, or starts to improve, lack of activity will eventually make the patient worse. Depending upon the degree of physiological brain dysfunction, patients should start to increase stressors slowly even if this means a temporary setback. This is neither an easy nor a fast process and again, depending upon the degree of brain dysfunction, may take years until the patient can resume a relatively normal life activity. (3) If the M.E. patient conforms to the guidelines set out in this definition, the insurance company can only make the patient worse by instituting progressive aggressive forced physical and intellectual activity. M.E. is a variable but always, serious diffuse brain injury and permanent damage can be done to the M.E. patient by non-judicious pseudo-treatment.

**J. Sleep Dysfunction:** Many M.E. and CFS patients have multiple medical problems giving rise to their illnesses. Our office has in a few cases found up to 20 different pathologies and pathophysiologies in a single patient. The cumulative pathological weight is sufficient to cause any patient significant and chronic disability. One of many common problem areas is the nasopharynx and temporomandibular joints, a.k.a. the mandibular or jaw articulation. Several M.E. and CFS patients have significant pharyngeal and other obstructive airway problems that prevent adequate sleep function that in turn causes chronic fatigue syndromes and the associated chronic decrease in physical and cognitive stamina. Some of these correctable nasopharyngeal problems are so simple as to be mind-boggling. They include treating (1) enlarged tonsils that obstruct the respiratory tract when sleeping by surgery, (2) treating nasal obstructions, (3) treating chronic sinusitis with night time post nasal drip, and understanding (4) anatomically small pharyngeal box, (5) palate dysfunction and (6) temporomandibular dysfunctions that include mandibles that fall back to obstruct the pharynx when the patient sleeps. All M.E. and CFS patients should have a thorough investigation by an Ear-Nose-Throat specialist. Although it is costly, all M.E. and CFS patients should have a qualified orthodontist familiar with this group of illnesses carry out a careful examination of all M.E. patients. Unfortunately, sleep dysfunction testing and treatment is still at an early stage of its development. It is my experience that too often, when a sleep physiology physician finds a sleep dysfunction not related to obstructive disease or a movement disorder, he has little useful to offer in the way of treatment. Some sleep pathology physicians do go beyond this limitation and it is worthwhile for the treating physician to search for these rare individuals.

**K. Viral, Hormonal and Age Related Triggers:** I have discussed this briefly in the definition. This is a concept that is increasingly well known in medicine but to my knowledge has not been applied to M.E. Viral triggers are considered to be a possibility in certain asthmatic conditions, in multiple sclerosis, celiac disease and various rheumatoid conditions. All of these could be considered to be autoimmune illnesses. From examining hundreds of patients with fibromyalgia-like syndrome I cannot also wonder if NSAIDS, non-steroidal-anti-inflammatory drugs, that are increasingly prescribed for any pain condition, do not reset the CNS brain sensors to pain, thus creating chronic fibromyalgia and other pain syndromes. If this is proven to be true, then we can add pharmaceutical

triggers that we already know can provoke rheumatoid disease. I have mentioned elsewhere the relationship of anti-depressive medication in causing or worsening heart dysfunctions, fatigue syndromes, sleep dysfunctions but they are not the only ones. Antilipid (cholesterol) pharmaceuticals appear to cause significant muscle weakness and joint and muscle pain in many M.E. patients, much more than in the general population.

**L. Multiple Disabling Pathologies:** Most M.E. patients have multiple disabling pathologies and it is insufficient for any physician who finds one pathology to assume he has found the one and only cause of this complex illness. Too often I have seen physicians who have found one major cause of M.E. or CFS dysfunction and illness, treat it, and then criticize the patient for not getting back to work when in reality, what the physician uncovered was only the tip of the iceberg.

**M. Test Result Validity:** When I was a medical student at the University of Toronto, our radiology professor insisted that as physicians, it was important to go over the actual X-Rays of the patient with the radiologist in order to develop an understanding of how to read an X-Ray and how to keep the radiologist aware of the pathology that you are investigating. Over the years I have had multiple reasons to visit a radiologist to assist me with reading routine X-Rays, complex intestinal X-rays, Ultrasounds, MRI and CT scans as well as brain SPECT and brain PET scans. I cannot recall a single time that the radiologist did not take the time to go over the actual scans and X-rays with me and answer my sometimes very rudimentary and facile questions. However these trips to the hospital have also made me realize that the radiologist can miss major problems since they are not always aware of the individual patient's pathology. Recently, many SPECT scan and other technological facilities in Canada have simplified their technology, limited their findings to reports and failed to reproduce print-outs of their findings. This is true in Carotid and Transcranial Doppler examination where the velocity of blood flow through the arteries is not given, yet this is a valuable aid to understanding diseases related to arterial spasm. Yet the work sheets of the technicians contain this data. The same is true of the reading of EEGs. Neurologists too often simply say a test is normal since there is no evidence of a seizure disorder or a large space-occupying lesion. Often the neurologists go no deeper than this and miss major observable pathology. It is most unfortunate that so few centers

have adopted QEEG or Beam technology, i.e. quantitative computer driven EEG technology. It gives significant better understanding of brain function abnormalities. The same is true of brain SPECT scans. These are very easy to learn how to read. I have already mentioned the problem with dropping Xenon scans. But recently, some Canadian centres have lost their experts in brain nuclear medicine and replaced them with individuals who are not expert in reading brain SPECTs.

They have also in some cases simplified the systems to maximize profit so that the detail is not always there. The hospital is paid the same for a badly done rushed SPECT as for an expert SPECT. This is increasingly a problem. For the physicians who only read the typed report stating, "the findings are normal" and who does not take the time to look at the brain images themselves, SPECT can be a useless exercise. I have mentioned the problem with thyroid ultrasound imaging. It is essential to insist that the radiologist actually give the measurements of each thyroid lobe rather than simply saying, "the findings are normal." This attention to detail is time consuming but also rewarding for the physician who is truly interested in understanding pathology.

**Definition Changes & Improvements:** As with all definitions, the Nightingale Research Foundation's Definition of M.E. will have to be looked at by many clinicians and researchers and increasingly knowledgeable patients and over the years, disagreed about, changed and improved upon. But what this definition does today is (a) separate clearly M.E. from CFS and (b) demonstrate that M.E. is an early diagnosable and provable disease - as are all true diseases, and (c) assist in the prevention and also the early treatment and cure of M.E. patients.

**This Nightingale Research Foundation's Definition will be available with any updates or corrections, on the Nightingale Research Foundation's Website, <http://www.nightingale.ca> This definition may be copied, translated, distributed by electronic or hard copy and may be included, in whole or in part in any publication without permission from the Nightingale Research Foundation or the authors, provided that this last paragraph and referral back to our website are noted. A copy of any translation should be sent to Nightingale for possible inclusion in our website.**

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