The Nightingale Research Foundation Definition of Myalgic Encephalomyelitis (M.E.)

Presented at the IACFS/ME, International Association of Chronic Fatigue/ Myalgic Encephalomyelitis Research & Clinical Conference in Ottawa Canada September 22-25, 2011

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The original 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, then 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 (ME), 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, Oldham West & 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*

* * *

At the first meeting on the 27th of October 2005, the Chairman of the Joint Committee, Dr Ian Gibson, asked me to prepare a report and definition that might assist the committee in its further deliberations. The following are my original recommendation. Dr Bruce Carruthers, who chaired the 2003 Canadian Clinical Case Definition for M.E./CFS, was also present when I gave this definition. I strongly disagreed with Dr Caruthers in the merging the definitions of M.E. and CFS since on the basis of the physical total body assessment of both M.E. and CFS patients; these two names represent two entirely different spectrums of illnesses. The present 2011 definition is confined to the defining of Myalgic Encephalomyelitis (M.E.). The term CFS is mentioned from time to time to clarify differences.

It is increasingly obvious that too much importance was being placed upon the definitions of Chronic Fatigue Syndrome (CFS), and not enough upon the actual disease, Myalgic Encephalomyelitis (M.E.). 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 and rational diagnosis as well as a scientific confirmation of any testable illness. Such is not true of M.E. where a rapid and rational diagnosis can be made that can be confirmed by laboratory and other technological testing.

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, Goldstein, J, Levine, P, 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., retaining the CFS definitions (Holmes, G.P.) (Fukuda, K) as a basis for such change. Such 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 representing many different illnesses**. At one of the meetings held to determine the 1994 U.S. NIH/CDC definition of CFS, in response to my question from the floor, Dr Keiji Fukuda stated that numerous M.E. epidemics—he 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:** The 1988 and 1994 NIH/CDC, Chronic Fatigue Syndrome (CFS) definitions have been interpreted by most psychiatrists and most main-stream physicians as a form of psychiatric disease. It has been suggested that senior medical bureaucrats at NIH /CDC from the beginning, saw these so-called CFS patients as a form of psychiatric illness. In effect, the NIH/CDC definitions and their progeny have done an injustice to both patient and physicians who understand the physical basis of both M.E. and the pathologies of the several disease entities that fall within the CFS definition umbrella. In my 27-year investigation of M.E. and CFS patients, I can state with clarity that there is less psychiatric disease among M.E. or CFS patients than in the general public.*

Preamble to 2011 Definition of Myalgic Encephalomyelitis (M.E.)

Precursors to illness

Epidemic and Non-Epidemic cases of M.E. are often preceded by repeated minor infections. This might suggest either a vulnerable immune system, or an immune system subject to overwhelming stressors such as:

- repetitive contact with a large number of infectious persons,
- long hours of exhausting physical and / or intellectual work,
- physical traumas particularly to the head and neck,
- immediate prior immunizations, particularly if given when the patient has: **(i)** concurrent allergic or **(ii)** autoimmune or **(iii)** infectious disease or **(iv)** if the patient is leaving for a third world country within 3-4 weeks of receiving any immunization, *(See The Lancet, Poliomyelitis and Prophylactic Inoculation, Dec. 15 1956)*
- neuro-vascular-tropic epidemic disease in a susceptible host,
- exposure to chemical or metal toxin,
- environmental travel anomalies & exposure to novel infections,
- the effects of starvation diets and privation
- variability in genetic resistance.

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 pathological entity and separate out illnesses with a similar symptom picture? Only then can the physician:

- properly understand the patient,
- provide reasonable advice,
- hopefully provide effective treatment before the illness becomes chronic
- if necessary, call in an appropriate specialist
- direct research into investigating the same pathology and hopefully reversing patho-physiological injuries

This definition assists in all of these areas.

General Information

(1) Myalgic Encephalomyelitis is **(a) an acute onset, (b) biphasic (c) epidemic** and endemic (sporadic) contagious illness, with a **(d)** minimal **incubation period of 4-5 days** that **(e)** spreads easily to both children and adults. In most M.E. epidemics the affected age group is over 20, so it is obvious that this is a rapidly mutating virus or the patient has not previously contracted this virus and has developed no previous immunity. Since 1934, M.E. has been associated with over 60 epidemics worldwide. In M.E. there is always a persistent diffuse vascular injury of the CNS measurable in the acute and chronic phase. Chronic M.E. affects the body's metabolic and control mechanisms.

(2) First Phase: Although the relatively mild onset disease can vary, in most cases the first phase tends to be a banal, mild flu-like illness lasting 2-5 days followed in most cases by a short apparent recovery at which time the second and significant disease phase occurs. Infrequently the first phase may be so mild that it is not recognized.

(3) Second Phase: The second phase of M.E. represents a **measurable vasculitis** with or without associated pain and a measurable **diffuse vascular encephalopathy.** In those with an associated significant pain syndrome, there is both a **diffuse encephalopathy plus a posterior myelitis** from which the illness takes its name, encephalomyelitis. It is this second persistent phase that most characterizes M.E.

(4) Pain Syndromes: The various pain syndromes are highly variable and include head, chest, gastric, hepatic, bladder, vascular, migratory muscle and arthralgic pain, cutaneous hypersensitivity and malaise but the more severe symptoms tend to be reserved for the second phase of the M.E. illness. Pain syndromes are either neurological or vascular in origin. *(See Clinical and Scientific Basis of M.E./CFS, Chapter 13, pps. 124-126)*

(5) Late Summer Peak: Although the illness can occur at any time of the year, epidemics and endemic cases in the North Temporal zone tend to **peak in the late summer.** Epidemics when they occur, (if they are followed) may grumble on for 2-4 years or longer in the general community.

(6) This **(i) biphasic nature** of M.E., **the (ii) short incubation period of 4-5 days,** and the **(iii) peak period in late summer, (iv) lack of prior immunity in the over 20 age group** excludes most viruses.

(7) As in all infectious diseases, this virus causes a wide degree of injury from:

- **Non-symptomatic and/ or infectious carrier states,**
- **Mild:** in which the patient recovers without any sequellae, is never investigated and is usually given the diagnosis of mild "flu",
- **Chronic:** where the patient is diagnosed with M.E. or
- **Death:** in an autopsy the pathological diagnosis is given and the cause of severe M.E. is missed. In at least four published M.E. epidemics deaths has occurred.

(**8) Cohorts may develop different non-M.E. type autoimmune and malignant diseases** that may not be recognized or diagnosed until later in the illness. The following four findings, noted immediately below, occurred in either or all of the 1984 **(i)** Lake Tahoe, **(ii)** South Carolina and in the **(iii)** Ottawa & Quebec area late summer epidemics and in **(iv)** John Richardson's clusters in Newcastle-upon-Tyne both in 1984 and earlier case studies. The same virus may have the capacities to cause significantly different diseases. These autoimmune and malignant cohort diseases include:

- Viral myocarditis resulting in heart transplant or death
- Type-1 diabetes (siblings may develop concomitant classical M.E.)
- Autoimmune diseases: thyroiditis, interstitial cystitis, Sjogrens & colitis
- Malignancy: **(a)** thyroid malignancy and **(b)** various blood malignancies are common late associations with M.E. epidemic patients.

The associated spectrum of cohort illnesses, further define the viral cause of M.E. illness. I know of only one viral family that can typically provoke all of the above findings, and that is the enterovirus family.

(9) As in all infectious diseases the degree of illness in M.E. is highly variable. Depending upon the hosts **(a)** age, **(b)** sex, (c) genetics, **(d)** severe prior exhaustion, **(e)** preexisting pathologies & infections or **(f)** immediate prior immunization, vary the actual degree of illness considerably. **(g)** Different viral genomic subtypes of the same or similar virus and **(h)** quantity of viral load received on infection can vary the degree of illness.

(10) Youths, independent of the degree of brain SPECT changes, tend to have a better chance of reasonable recovery than adults with the same degree of SPECT changes.

Note: Many of the abnormal symptoms and findings noted tend to improve to various degrees, some over months, some over a few years. Also with time, many patients tend to compensate for these pathologies if the patient's social and financial structures permit. Unfortunately, the M.E. patient rarely returns to the previous normal level of activity and ability and those severely damaged in the second stage of the illness rarely can return to the competitive world. At times apparent recoveries can be followed years later with a resurgence of the phase-2 disease process.

The Nightingale 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.)

Note: *This is a definition of Myalgic Encephalomyelitis (M.E.) This is NOT a definition of CFS.*

1. M.E. is a **(a)** variable and **(b)** biphasic acute onset **(c)** endemic and epidemic infectious disease with a **(d)** minimal incubation period of circa 4-5 days infecting youths and adults, but the **(e)** significant patient population is over the age of 20, individuals who have not acquired specific immunity. Epidemics tend to be seen first in institutions, schools, hospitals, or in other places of crowding such as barracks and following long bus trips. This suggests a virus that tends to mutate rapidly or one that does not concur lasting immunity.

2.Acute Primary Infection Phase: the first phase is a highly contagious and passed by oral or fecal route. In most but not all cases a mild to modest URTI or other infection is evident. In most cases this acute phase infection tends to improve after 2-5 days and if the patient was ill enough to stop their activities, the patient may improve sufficiently to return to school or work for a few days or less. Rarely has any significant increase in temperature been observed. Significant pharyngitis has rarely been documented. On some occasions the acute primary phase is so mild it may be missed.

3. Mild to Modest Chronic Phase: This normally occurs within 2-7 days of the relative return to activity following the acute phase. This phase is characterized by severe neurological and symptoms of muscle weakness after modest exercise and frequently significant pain syndromes that do not seem appropriate to the relatively mild to moderate measurable CNS changes noted on routine physical examination. This may lead to the physician believing this to be an over-demonstrative or anxious patient. Subnormal and fluctuating basal temperatures are common or the rule. During and after this period many patients tend to have a decreased ability to adjust to ambient temperature change. However there are often significant measurable findings in both epidemic and endemic situations if the following tests are performed at onset of illness:

a. positive oligoclonal banding suggesting CNS protein injury,

b. elevated spinal fluid pressure

c. abnormal EEG,

d. significantly abnormal brain SPECT & vascular encephalopathy

e. enteroviral gastritis.

4. Severe Chronic Phase: Severe changes are easier to observe in epidemic situations and sometimes dismissed in endemic cases due to the relative lack of obvious findings on physical examination. These changes may simulate poliomyelitis or MS. In severe cases the patient is usually diagnosed with another illness rather than severe M.E. When deaths occur in M.E. they are diagnosed with the appropriate autopsy report related to CNS damage or heart failure and their illnesses tend not to be associated with M.E. It is a fallacy that deaths do not occur in the acute phases of M.E. Both CNS and cardiac deaths have been documented in epidemic and endemic M.E.

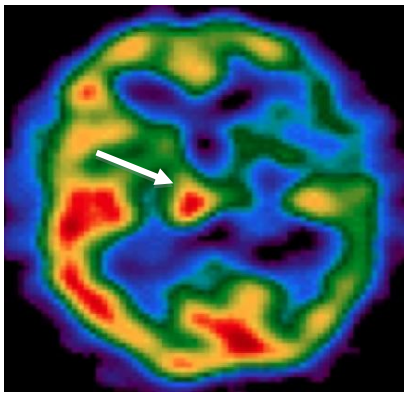
5. M.E. is a measurable diffuse vascular encephalopathy. This can be demonstrated on testing. Observable changes may vary depending upon the length of time since illness onset and degree of illness. All modest to severe M.E. patients have changes in their brain SPECT examination. (NOTE: Physicians should learn to read brain SPECTs themselves and discuss the findings with the neuroradiologist.)

Type 1: one side of the cortex is hypoperfused, frequently one side of the basal ganglia are either not observed or are significantly diminished. Mild one-sided changes where the SPECT architecture is not significantly distorted may be associated with spontaneous recovery. Severe one-sided focal hypoperfusion, where the SPECT architecture is significantly abnormal is often diagnosed as encephalitis or mis-diagnosed as malignancy, particularly when the changes are focal. Some of this group may demonstrate moderate or complete recovery.

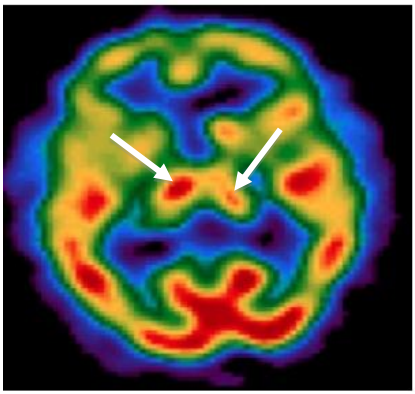
Type 2: Where both sides of the cortex are hypoperfused or injured there is little chance of spontaneous recovery. (Patients who have both basal ganglia hypoperfused have been observed to develop Parkinson's disease, years later. There simply have been too little long-term follow-up of endemic and epidemic

M.E. patients to ascertain whether this is coincidental. However in the Akureyri epidemic 3 children died of Parkinson's d.) Many patients with bilateral cortical perfusion anomalies tend to develop moderate dysautanomia. (In my 1984-5 epidemic group I have two Parkinsonian patients.)

Type 3: When the cortical SPECT architecture is totally distorted, the patient rarely recovers. In this group we also tend to see severe changes to the posterior chamber organs, the Pons, the Cerebellum and sub-cortical and brain stem structures. This group of patients, tend to develop severe dysautanomia, POTS and other organ and system pathologies. It is among this group where we tend to see bed ridden or house bound patients. Children with this type of injury have been known to be treated as though they suffered a psychiatric manifestation.



Original SPECT



Two years later

The above brain SPECTs were supplied by Dr Vance Spense of Scotland. The first image was taken earlier in the M.E. diagnosed illness and the second taken two years later. In the first image there is no indication of the right basal ganglia (In SPECT, the images are reversed). and in the second image the right basal ganglia is still intact and now the one can faintly observe the left basal ganglia. This is a typical M.E. patient brain SPECT image showing improvement over two years but remaining basal ganglia dysfunction.

6: Neuropsychological Testing: Several neuropsychological changes have been noted that suggest significant abnormality as noted by Dr Bastien. *(Bastien, Sheila. The Clinical and Scientific Basis of M.E./CFS. Chapter 51, pps. 453-460)*. These changes often correlate with brain SPECT changes:

a. Tactual Performance Test: (TPT) 59%,

b. Decreased fine and gross motor problems,

c. Impaired bilateral motor test scores,

d. Abnormal figure drawings,

e. Spatial perception dysfunction,

f. 40% or more have abnormalities of immediate visual recall, Tap N-Dom, Grip N Dominance, & grip dominance problems

g. Word finding problems,

h. Subtle problems with receptive and expressive aphasia,

i. Impaired Wechsler Memory Scale 85%, with short term memory loss,

j. Decreased IQ on expected WAIS-R,

k. Impaired MMPI measurably different from depression,

l. 20% of pre-illness IQ is routinely lost, performance IQ exceeds significantly loss of verbal IQ,

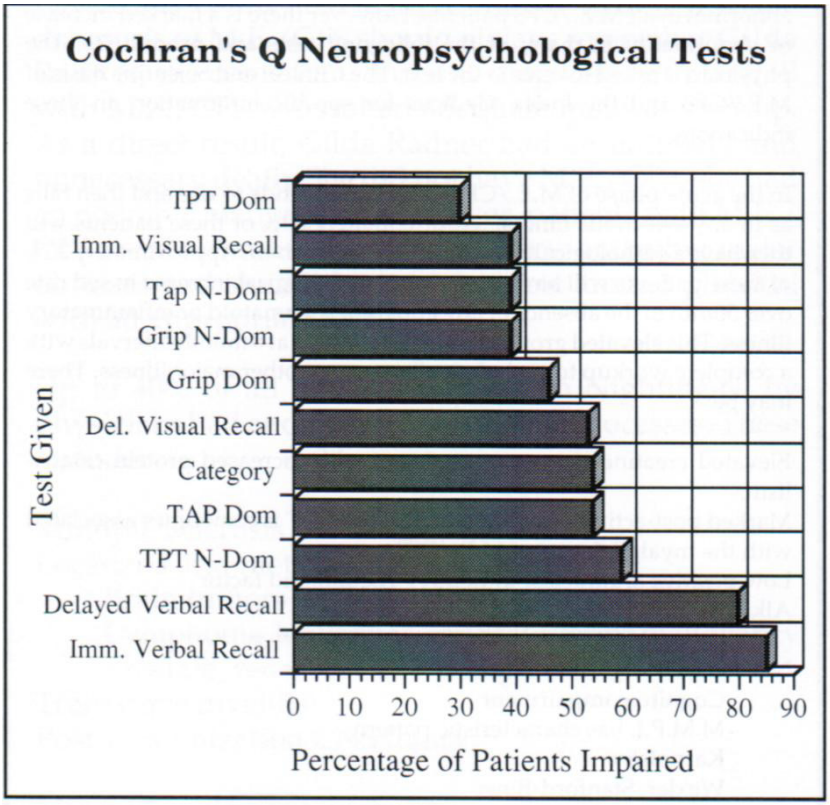
m. Dyscalculia,

n. Abstract reasoning dysfunction,

o. Easily distracted, significant difficulties processing multiple tasks simultaneously,

p. Significant comprehension disability in the presence of multiple auditory signals,

q. Sequencing problems. In Cochran's Q Neuropsychological tests there are increased problems in both immediate and delayed verbal recall.



7: Second Phase Pain Syndromes: Some M.E. patients do not have pain syndromes and this is probably due to little or no involvement of the spinal cord and its appendages. **(Comparison Note:** M.E. is **not** caused by the three Polioviruses although antibodies to polio 1, 2 and 3 often significantly increased during the first years of illness, as are most antibodies to common past viral infections, mumps, rubella, EBV.) However, **M.E. without pain** can be equated with mild Bulbar or mild CNS type Poliomyelitis. **M.E. with pain** can be equated with brain injury plus **posterior** spinal poliomyelitis). **Second Phase Pain Syndromes**, particularly during the first months of illness should be sufficient to alert the physician to the diagnoses of M.E. encephalopathy and may include any or all of the following:

a. Post-Exertional Malaise *(inability to recover within a normal period after exercise) is often quoted as a cardinal feature, however, it can be missing in some severely disabled M.E. patients with inability to exercise or even walk such as many patients with dysautanomia.*

b. Resting Malaise *that can be severe even on resting; Severe cutaneous hypersensitivity often described as malaise and sometimes formification in the early months of the disease, sometimes diagnosed as fibromyalgia, this may be a vascular anomaly,*

c. Headaches & Head Pain: *Severe persisting or recurrent headaches suggestive of encephalitis, or described by the patient as a type never previously experienced,*

d. Specific Head Pains: (i) *Retro-orbital eye pain,* ***(ii)*** *occipital area pain, (iii) ear pain with presbycusis,* ***(iv)*** *assessory nerve pain*

e. Neck pain *associated with neck rigidity and occipital pain,*

f. Causalgia, *an intense burning pain,*

g. Gastric area or hiatal area pain *that may simulate cardiac angina,*

h. Migratory muscle & arthralgia pains, *lasting seconds or hours,*

i. Muscle Spasm Pain *particularly in the areas of circular rings of muscle, such as the ear, the eye, the lower esophagus, the anus and the urethral of vaginal area,*

j. Interstitial cystitis with vascular changes in bladder: *in the early months of the disease many women experience bladder area spasm and interstitial cystitis with no abnormal bacterial growth in the urine but a tendency for increases in urinary red blood cells,*

k. Muscle spasm *with visible tics in the muscles of the extremities can be spontaneous or associated with increased activity,*

l. Localized short term nodular pain *immediately above & medial to the heart. The nodule is superficial & can be rolled under the finger,*

m. Fibromyalgia type pain *may simply be due to total body hypersensibility,*

n. Bornholm disease*, intercostal myalgia,*

(See Clinical and Scientific Basis of M.E./CFS, Chapter 5, pps. 58-62)

All of these pain syndromes can be highly variable, even over a few minutes or hours and tend to decrease or disappear with time. This extreme variability may cause the physician to believe the patient is simply experiencing an attack of anxiety neurosis. The patient can be so alarmed to be terrified and mis-diagnosed as a case of hysteria, particularly after minimal tests do not support physical diagnoses. Most severe Second Phase Pain Syndromes are gone or are bearable within two years. The physician may mistake the decreased pain levels with recovery. If the pain syndromes do reoccur with forced physical or other activity they are rarely as extreme as at disease onset.

> **IMPORTANT NOTE:** many physicians prescribe narcotics, analgesics or NSAIDs for these second phase conditions, often with an open prescription attitude. This can be dangerous: **(i)** Narcotics significantly depress the central respiratory centres and since these patients frequently have low oxygen saturation levels below 88% to begin with (i.e. below 88% equals loss of consciousness), subsequent worsening brain dysfunction occurs and deaths have occurred; **(ii)** NSAIDS can cause vasculitis and in my experience on going NSAIDS can provoke fibromyalgia; **(iii)** patient self-prescribed over the counter medications including ASA and low grade codeine combinations can cause presbycusis, vertigo and GIT bleeds.

8: Testable Major Sleep Dysfunction: Measurable sleep dysfunction occurs beyond the multiple patient complaints of (i) lack of restful sleep, (ii) waking exhausted, (iii) extreme nightmares early in the disease, (iv) sleep reversal. Some of the measurable findings include:

a. impaired sleep efficiency,

b. significant fragmented sleep architecture,

c. movement arousals, *particularly with associated pain syndromes,*

d. Deep Sleep: *the majority of M.E. patients have an absence or no significant type 3 and 4 deep sleep,*

e. Abnormal REM *sleep pattern, delayed, shortened or absent,(REM is essential for short term memory)*

f. Oxygen Lack: *A portion of these M.E. patients experience significant measurable oxygen lack during sleep. If oxygen saturation drops below 92% this is sufficient to cause night blindness. If the sleeping oxygen level drops below 88%, this is sufficient to cause loss of consciousness rather than sleep. (In our study of 53 patients with M.E. or CFS 25 of the patients (47%) fell below 92% and a further 17 patients (32%) had an oxygen saturation level that fell below 88%.* ***(Repeat Note: Narcotics*** *should be avoided in M.E. patients. Patients on narcotics for severe pain syndromes were not included in our studies since narcotics further depresses the respiratory centres and may lead to death or worsening oxygen saturation.)*

g. Hypnagogic & Hypnapagogic *dysfunction,*

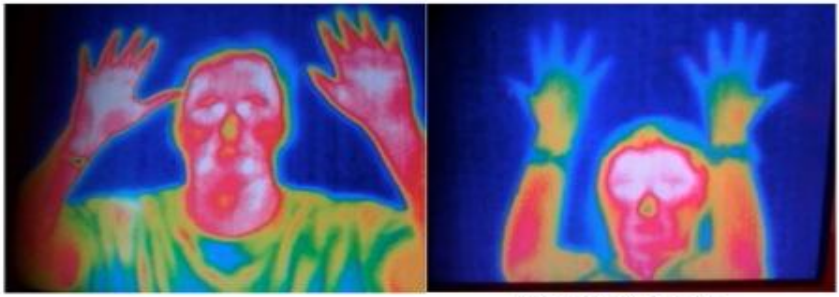
h. Von Economo Encephalitis-like Syndrome: *A few M.E. patients have such severe hypersomnia that they can be confused with a form of Von Economo's encephalitis. These patients may sleep up to 20 hours a day.*

9: Vascular Dysfunction: This is one of the most obvious dysfunctions seen in M.E. patients when looked for and probably is the cause of a significant number of M.E. complaints. 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 patho-physiology 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. Measurable vascular changes are seen in the following commonly occurring physiological changes:

a. POTS: *Severe orthostatic tachycardia syndrome: the patient experiences rapid change in heart rate and the fall in blood pressure when standing. Often dismissed as due to inactivity.*

b. Cardiac Irregularity: (i) *inability of the heart to increase or decrease physiological speed and pump volume in response to increase or decrease in physical activity,* ***(ii)*** *various cardiac irregularities on 24 hour Holter monitor in some patients,*

Thermogram



Healthy Father

Daughter with severe Raynaud's

c. Reynaud's Phenomena: *is typical in M.E. patients with vasoconstriction, blanching, cold and pain of extremities. This is the cause of temperature dysfunction in many M.E. patients and their inability to adjust for changes in ambient temperature. When patient is visualized on a thermogram (infra-red) the extremities are poorly visible when compared to a control person. See girl with M.E. below with minimal circulation in fingers and significantly decreased in hands and arms when compared with her normal father. This condition is also associated with vascular pain.*

d. Severe Sweats: *These sweats resembling menopausal complaints occur in both male and female M.E. patients and cause may be either endocrine or vascular.*

e. Ehlers-Danlos Syndrome (EDS) : *Frequently diagnosed as M.E. This is a group of genetic illnesses has different forms. Cases appear in late teens, early thirties following what appears to be an infectious injury. There are a spectrum of similar but probably unrelated conditions that include* ***(i)*** *Hyper-reflexia syndrome (a common M.E. associated condition),* ***(ii)*** *EDS & (iii) Marfan Syndrome. All three are connective tissue disorders with increasing elasticity of the arterial system as well as joints, climaxing in Marfan Syndrome that can lead to early death due to extreme hyper-elasticity of the ascending aorta and resulting aneurysm. (Brucellosis, which can also cause M.E. may cause death due to ascending aorta hyper-elasticity and aneurysm if not recognized early and appropriately treated. Additional generalized features of this spectrum of illnesses include* ***(iii)*** *India rubber or hyperelastic skin,* ***(iv)*** *easy bruisability (vascular fragility),* ***(v)*** *Arachnodactyly (long spider- like fingers). (For more on EDS see discussion to follow.)*

f. Circulating Blood Volume Decrease: *This is a testable nuclear medicine test of significant value. As some patients improve their circulating blood volumes also improve. Some patients have less than 50% of their normal expected circulating blood volume. These patients may have no significant or any associated anemia.*

g. Acetylcholine (Ach) mediated vasodilator pathway. *(See Discussion)*

h. Clotting Defects: *There is a significant group of M.E. patients who may have either arterial or venus clotting defects or both. This tends to be a genetic disorder and any M.E. patient with a family history of early stroke, Transient Ischemic Attacks (TIAs), myocardial infarct, pulmonary embolism should be checked for both groups of clotting effects. It is essential to also order cardiac, carotid and transcranial Doppler tests on these patients and on their relatives. You may save more than one life. 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. Persantine Effect in M.E. Patients: *Persantine is a chemical manufactured by Boehringer Ingelheim that dilates both peripheral and cardiac blood vessels, causing the heart rate to increase as in a POTS patient. 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 particularly those with fibromyalgia it can cause severe muscle pain involving the entire musculature. Normally this can be reversed by injection of an antidote but this does not always work rapidly in M.E. patients. Severe Persantine pain and fatigue can be intolerable and persist for minutes to days in some M.E. patients following Persantine use. It does not tend to occur in non-M.E. patients.*

NOTE 1: *The Persantine test is the best test to diagnose Fibromyalgia but can be extremely painful. In effect it demonstrated one of the major causes of Fibromyalgia,* ***vascular pain****.*

NOTE 2: *A similar curious test is the* ***mistaken*** *use of Ampicillin or its analogues to treat severe pharyngitis when in effect the physician has misdiagnosed a virally induced EBV, (infectious mononucleosis). When this group of antibiotics is employed it causes a fulminant measles-like rash over the entire body, often mistaken as a penicillin allergy.*

10: Endocrine Dysfunction: This is a late but common finding in many M.E. patients and includes:

a. Pituitary-Thyroid Axis: *Physicians tend to use the usual indicators of thyroid and parathyroid pathology to confirm thyroid disease. These are changes in serum thyroglobulin, TSH, FT3, FT4, Microsomal Ab., PTH, calcium and phosphorous. Unfortunately, these tend to be poor indicators of early thyroid disease. The Mayo normal adult female thyroid volume is given as 6.5 to 10.5 cc. and 7.5-11.5 cc. in male patients. They are a better indication of early pathology. (Mayo Clinic averages) (Rumack, Carol). The minimal average thyroid volume in a female is 6.5 cc but until the thyroid shrinks to below 4-5 cc there tends to be no abnormal change in any of the above usual thyroid tests. If a patient is being treated with thyroid medications or taking over the counter alternative medications containing thyroid, the thyroid will shrink and this test is not useful. If an annual thyroid ultrasound at the same ultrasound clinic is seen to be shrinking or enlarging beyond the MAYO normals then you may well be seeing the early thyroid injury developing.* ***Physicians should always ask the reading physician to give the thyroid volume when thyroid ultrasounds are ordered.*** *Otherwise the volumes tend to not be given. The notation of "normal thyroid volume is not sufficient.*

b. Thyroid Malignancy: *Significant increased risk of thyroid malignancy which may occur at any time after the initial illness. Serial thyroglobulin analysis may suggest this but thyroid ultrasound with needle biopsy of all single nodules over 1cm or smaller nodules when they are significantly hypervascular is the single most important investigational tool. TSH, FT3 & FT4 are usually normal. (Normally, thyroid malignancy occurs in 20-30 patients per 100,000 in the general population. We examine every M.E. patient for thyroid malignancy by ultrasound and needle biopsy for suspicious cases and our findings of thyroid malignancy in M.E. patients exceed* ***6,000 per 100,000****.)*

c. Thyroid volume changes*. If an annual thyroid ultrasound is performed the physician should always ask for volume of each lobe and compare this finding with previous measurement to determine rapidly enlarging or shrinking thyroid volumes. If not requested in our experience thyroid lobe volume is usually not given. (TSH, FT3 & FT4 findings tend to remain normal during obvious thyroid changes, unless the thyroid volume shrinks to below 4.0 cc) (The normal MAYO clinic female thyroid volume is 6.5-10.5 cc and for males 7.5-11.5 cc) (****Note:*** *When on thyroid medication, the thyroid shrinks and this measurement cannot be employed.).*

11: Depression, Anti-depressive Medications and M.E.

M.E. is not depression, hysteria or conversion disorder. Nor is it a somatization disorder; M.E. is a measurable acute onset diffuse vascular injury of the brain. Depending upon the areas of the brain and the degree of injury different organ and system injuries may follow.

The following list may help distinguish M.E. from depression and is abridged in part from the work of Dr J. Goldstein and Dr L. Inger:

a. *History: relative absence of family history of psychiatric disease, suicide, crime, psychiatric hospitalizations.*

b. *Achievement: many adult M.E. patients have a history of significant academic, and financial achievement. Although this does not rule out psychiatric disease, achievements can weed out psychiatric patients.*

c. *M.E. has a characteristic MMPI profile, with elevation in scales 1,2,3,7 & 8. The depression profile is 2 or 2,7 or 2,4,7.*

d. *M.E. patients tend to have an intrusion of Alpha waves unto Delta slow wave sleep. Patients with Bipolar or Monopolar Depression (MDD) have decreased REM latency and increased REM density.*

e. *Corticotrophin Releasing Hormone test tends to be normal or elevated in M.E. patients but decreased in MDD.*

f. *In M.E. there are memory deficits in stimulus registration and encoding consolidation, over estimation of ability. In MDD there is slow response time and underestimation of ability in memory testing.*

g. *In M.E. patients QEEG/BEAM scans demonstrate temporal lobe dysfunction on AER & VER.*

h. *Usually alcohol intolerance and avoidance in M.E. patients. In MDD patients there is no alcohol intolerance and, at times, alcoholism.*

i. *Fibromyalgia is frequent in M.E. patients and rare in MDD patients.*

j. *An abnormal 2-5 A Synthetase/RNase L pathway in M.E. consistent with a chronic viral infection. This is not usually seen in MDD patients.*

k. *In M.E. there tends to be a reactivation of antibodies to most common historical viral infections. This is not a usual MDD finding.*

l. Antidepressive medications rarely are of assistance in M.E. patients. Sometimes very low levels may help sleep function. In MDD patients can significantly improve the MDD patient's well being.

Discussion & Differential Diagnosis of M.E.

This discussion refers primarily to M.E. and NOT to CFS.

Any attempt to develop a workable definition of M.E. is fraught with multiple seemingly insurmountable difficulties.

I have laid out the basis for considering the three 1984 epidemics in (i) Lake Tahoe area, (ii) South Carolina and (iii) Ottawa & Quebec were caused by the same viral injury and the evidence leads only to enteroviruses due to their rapid 4 day transmission, the cohort illnesses, the excellent work of Dr Bernadette McLaughlin of the Ontario Government Viral laboratory in Toronto. There is also the simple fact that in all of the 60 plus M.E. epidemics only in four has the same virus been recovered and they were all enteroviruses. Enteroviruses, whether Coxsackie, ECHO or Poliovirus, historically have been very difficult to recover in a live patient. It has only been with the development of PCR technology that viral recovery and identification has been made easier. Recently, Dr John Chia has ably demonstrated the anatomical proof of chronic enteroviruses in M.E. patients. Prior to this Dr Len Archard of Kings Cross Hospital, London demonstrated the same enteroviral finding in M.E. patients.

Section 1

Lack of Detail: With the exception of the 1934 L.A. Epidemic, the 1955 Cumbria and the Royal Free epidemics, few of the other many excellent epidemic studies are sufficiently complete to provide comprehensive information.

Long Term Follow-Up: The **(a)** two page, six-year-after, study of the Akureyri epidemic by Sigurdsson and Gudmndsson in the Lancet, **(b)** and 10 page, Hyde and Bergmann Akureyri study (43 years after the fact) edited by Jenkins and Mowbray, John Wiley and Sons book Post-Viral Fatigue Syndrome involved too few of the original epidemic population. The 10-page, 10-year after study of the Lake Tahoe epidemic by Peterson et al in the Journal of Chronic Fatigue Syndrome involve a relatively small population sample and no obvious in depth

organ and system investigation. In effect, no long-term studies have ever been made in any significant number of patients in the over 60 M.E. epidemics. It is therefore almost impossible to discuss the true long-term consequences other than in those patients who visibly remain chronically disabled.

In Depth Patient Investigation: Other than my own multisystem, multi-organ assessment of M.E. and CFS patients published in Missed Diagnoses by B. Hyde (Lulu.com), there is little in the literature to explore why these patients are persistently and chronically ill. No structured publication of the cause of persisting disability in either M.E. or in CFS patients has ever been published in any peer review journal. No study examining the late causes of disability, age and death of any significant group of epidemic patients has ever been investigated.

Funding: Other than the 1934 study, which first send Gilliam and then the Yale group to investigate, none of the other epidemic studies have been funded appropriately. Since 1988, much of NIH funding for CFS and M.E. appears to have been given to researchers not familiar with these patient groups or to researchers who are more interested in developing a psychiatric explanation. A review done in 1994 suggested a major part of the NIH funds for CFS were given to studies on Alcoholism and Fatigue, Psychiatric Disease and Fatigue, Malignancy and Fatigue.

Ridicule and Accusation of Hysteria: Many of the epidemic studies and the physicians who researched these epidemics have been met with ridicule. Fear of ridicule prevents both funding agencies and physicians from supporting any significant serious review of M.E. epidemics. Some notable physicians in the M.E. and CFS community have sustained unjustified ridicule by their colleagues. Few physicians are willing to continue the study of any disease process if they are unfunded and branded with ridicule. This is understandable; careers cannot easily tolerate ridicule. The disastrous blow by Colin McEvedy and Beard and to a lesser extent by Simon Wessley on M.E. research is evident. Unfortunately they are only the tip of the iceberg.

The 1988 & 1994 CDC/NIH Definitions of CFS: This definition invented by a group of individuals who as a whole had never clinically seen or investigated any serious number of M.E. or CFS patients has itself been a disaster to any serious M.E. research. This definition and its unloved children define no known patho-physiological illness.

Unfortunately due to this diagnostic profile, CFS, (which by definition is significantly different from M.E.) can be and has been readily interpreted by most physicians as a psychiatric phenomenon or worse, a joke.

Garbage Bag Disease: Unfortunately, many physicians appear to be using CFS as a convenient garbage bag disease, simply telling patients whom they have no time to investigate, "Oh, you have Chronic Fatigue Syndrome". It is most unfortunate that the Americans, who have now promoted the idea that CFS is the same as M.E., have only compounded the disaster. Due to this garbage bag phenomena mentality many CFS patients are never properly investigated for serious disease and most CFS patients have significant and often times treatable pathologies.

Section 2
The Infectious Cause of M.E.

During the period 1934 until the present time various infectious agents have been proposed as the cause of M.E. In the USA and elsewhere where CFS is also misconstrued as M.E. the following infectious agents have been linked at one time or another to these two illness groups. They include:

1. A variant of poliovirus
2. Enteroviruses, Coxsackie, ECHO, numbered & mutations
3. Epstein Barr Virus
4. Cytomegalovirus
5. SMON & Inoue-Melnick Virus (IMV)
6. Apollo Disease
7. Ross River Fever Virus
8. Ciguatera poisoning
9. Candida albicans
10. Human T Lymph tropic Virus I & II (HTLV)
11. Cheney-Bell-Defreitas-Terunuma Retro Virus

12. Mycoplasma fermentans & other subtypes
13. Foamy or Stealth Virus
14. BornoVirus
15. Human Herpes Virus & subtypes
16. Lyme Disease Virus (Borrelia burgdorferi & variations)
17. XMRV (mouse retrovirus)

Viral Cause: Almost all of these possible infectious and toxic sources have been championed as a cause of M.E. and of CFS by one person or a very small group of persons, or a private laboratory, most of them in the USA. Many of these individuals had a patent on the viral process and could potentially reap incredible funds by propagating false pseudoscientific data.

Some believe that one US government health official with his finger on the government funding cash pile, championed EBV for years due to his own fatigue syndrome. Then, when his EBV theory was found to be incorrect, those he funded appear to have blamed the patient of being psychiatric patients. Several of these infectious agents have been championed by private laboratories or university groups, which have patents, attached to the virus or the detection process or the treatment programs and so have used their theory as a potential cash cow. Several of these private labs also advertise a series of expensive complimentary tests and associated speculative and expensive treatment programs. Patient groups with little real knowledge of these infectious groups have been formed and resemble movie star fan clubs and are vociferous in pleading the cause of a particular infectious agent. Some commercial businesses holding patents on specific viral investigation processes even hold world wide conferences in which they pay university professors who can "prove" viral association of their pet virus with any number of illnesses. Such organizations can make it easy to invent proofs to improve one's CV and university tenure in the "publish or perish academic world". Some might consider the propagation of some of these infectious theories as possible fraud. One cannot underestimate the potential millions of dollars a private laboratory can recover by promoting these false viral theories. Individuals and companies have grown wealthy on the dissemination of possible false or spurious information about ME. and CFS.

The Enteroviruses: One has to cease believing that M.E. resembles or is the same as CFS. One has to cease believing those who patent virus and infectious agents for profit are necessarily going to tell the truth. If one looks only at M.E. and the diagnostic principles outlined above it is obvious that only one group of viruses can fit the picture as the causal agent of M.E. and those are the enterovirus family. There are no known patents on this group of viruses.

If one observes:

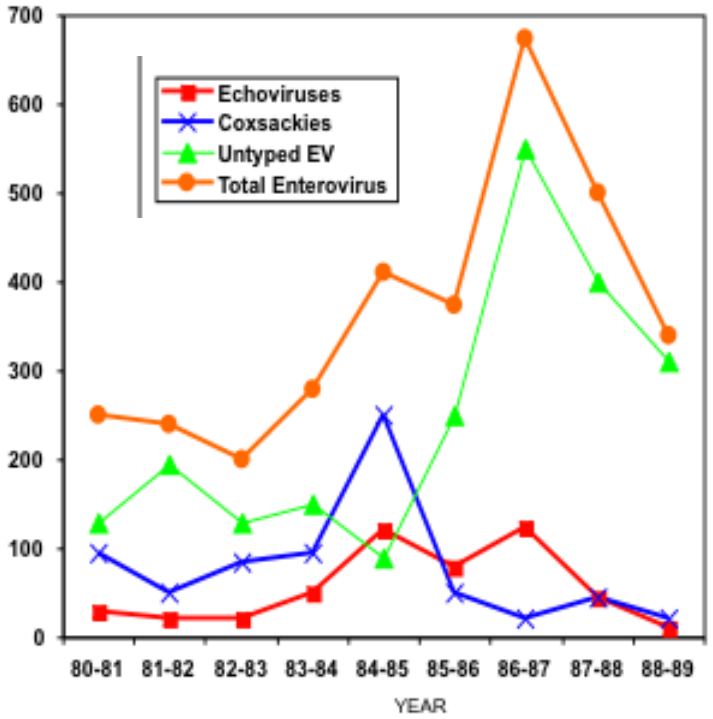
> ***a.*** *All three North American M.E. epidemics occurred at the same time, in the late summer of 1984 during the known peak phase of entero-viral infection. Originally, those who described their regional epidemic were not aware of the other two epidemics that occurred at the time;*
>
> ***b.*** *All three epidemics has similar if not the same features consistent with an enterovirus cause,*
>
> ***c.*** *The cohort diseases mentioned above were noted in one or all of the three epidemics are consistent with known enteroviral illnesses,*

It is hard to dismiss the enteroviral family as probable cause of this illness. But there are other reasons to believe this epidemic was due to enteroviruses.

This same epidemic & endemic occurred all over North America and Ontario during the same time period. In Canada we have free health care and free testing. Hundreds of Ontario doctors, independently observing seriously ill individual M.E. patients, initially assumed they were due to EBV and ordered EBV virus testing. Some may have picked up on the EBV theories already promulgated by Stephen Straus and his associates. Yet in the thousands of tests verified by Dr Bernadette McLaughlin at the Ontario Viral Centre, collectively she did not find any percentage increase in EBV recovery from these patients during the 1984-1989 period. During this period, Dr McLaughlin routinely sent the thousands of samples for a spectrum of other viral tests. Unfortunately testing was performed only during the endemic period from 1983-1989, at which time the Ontario Government stopped authorizing enteroviral testing as a cost saving measure. During this endemic period Dr McLaughlin found only one viral group responsible for the surge in fatigue and encephalitis related illnesses. The significantly increased viral recoveries were only enteroviruses.

In Ontario in the year 1984 & 1985 over 400 cases of enterovirus infections associated with fatigue illnesses were identified each year. This increased in the period 1986-1988 to over 500 cases per year and then dropped rapidly off. In 1984 the virus groups identified were the Coxsackie virus family. In the 1984-1986 period, ECHO viruses were recovered. However the biggest group of enteroviruses recovered during the period 1984-1989 were novel or untyped enteroviruses.

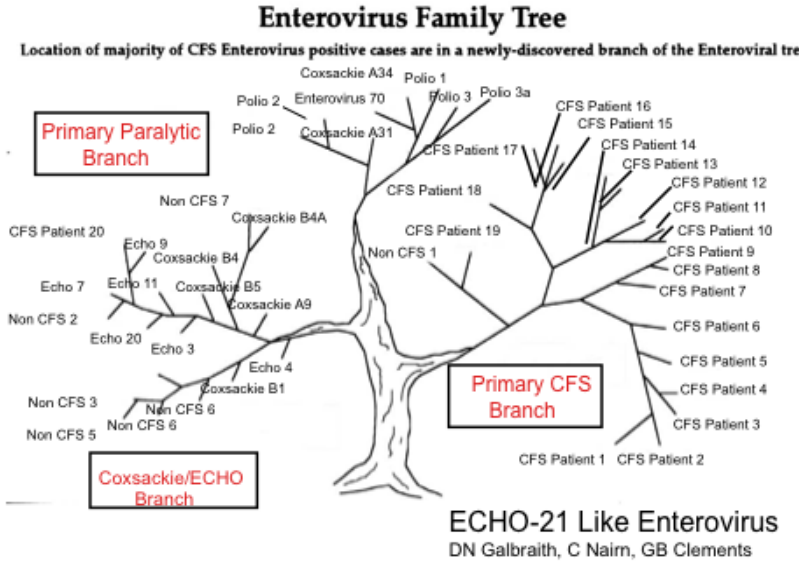
See graph that follows.



This graph represents the work by Dr B McLaughlin of the Ontario Ministry of Health in Toronto whose lab examined over 700 serum specimens submitted by Ontario physicians examining for both encephalitis and M.E. like illnesses in Ontario in the period 1983-1988.

The large number of untyped enterovirus is consistent with what was discovered in the Nightingale investigation of 100 M.E. and CFS Canadian patients tested in Glasgow at Ruchill Hospital, Scotland at the Scottish Enteroviral Centre. The following viral tree was from

Canadian M.E. and CFS patients from this period. **(a)** All acute onset patients that conformed to the above diagnostic criteria were M.E. patients and all **(b)** gradual onset patients who conformed to the 1988 & 1992 CDC diagnostic criteria were listed as CFS. Our Canadian patients were studied and produced the following enteroviral tree.



The above viral tree taken from Nightingale patients seen in Ottawa, Canada is the work of Drs Daniel N Galbraith, Carron Nairn and GB Clements at the Ruchill Hospital, Glasgow. Dr Nairn comments on the mutations in this group of viruses. (See J. Med Virol. 1999 July; 58 (3):304-12)

It is of interest that we supplied the Ruchill team with 100 of our endemic and epidemic Ottawa patients. Our sample consisted of 60 gradual onset CFS type patients and 40 acute onset M.E. type patients. We found **NO** enteroviral association in any of the gradual onset CFS patients. In the 40 acute onset patients the Ruchill group found that 20 of the 40 acute onset, or 50% diagnosed as acute onset M.E. were positive for enterovirus by PCR. It is obvious from these figures that if M.E. and CFS refer to the same disease process, then only 20% of the total group of 100 are positive for enterovirus. If the acute onset are considered to be M.E. patients, 50% of the patients were positive for enteroviral association.

Of interest, Stephen Strauss examined 100 CFS patients at Ruchill Hospital at the same time. In his study there was no enterovirus recoveries. I assume the patient group of Dr Strauss were either CFS or psychiatric patients or a mix of these patients. The gathering techniques of many NIH/CDC CFS studies may be considered suspect.

In my experience in a NIH funded laboratory, when I questioned their patients, they said they were in the US study due to an advertisement in a local newspaper offering free medical care to patients who conformed to the CDC/NIH CFS definition. Of course this group without insurance jumped at the idea of free medical care. In my estimation, this observation puts in doubt any NIH or CDC funded research.

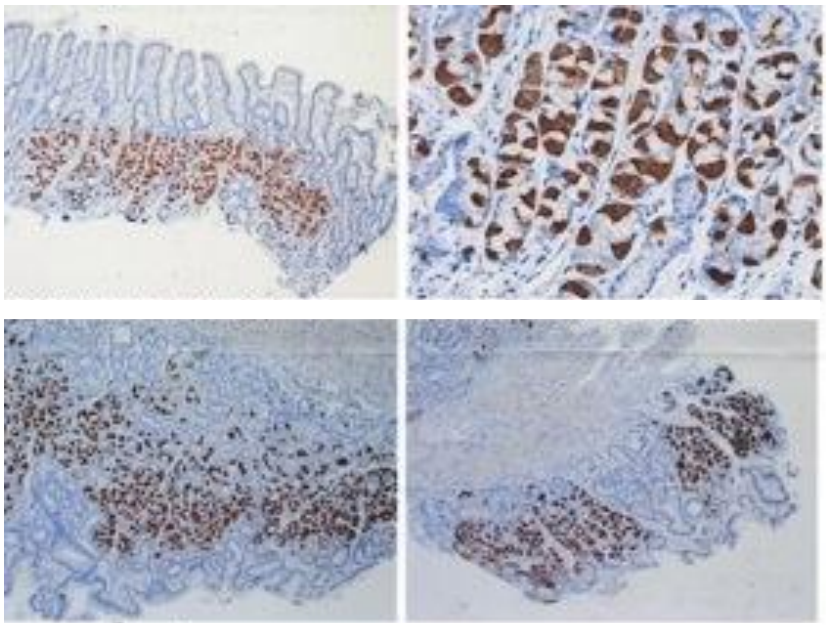
We believe that CFS illness usually represents missed major disease that would be diagnosed if a proper total body organ total system investigation were conducted. We also found that the Ruchill group failed to recover enterovirus in our previously positive same patients when they were tested several years later. Obviously with time, there is an increasing difficulty in recovering enteroviruses. However, positive virus results or not this group of M.E. patients were not significantly better.

See also: J Med Virol. 1995 Aug;46(4):310-3. Comparison of Coxsackie B neutralisation and enteroviral PCR in chronic fatigue patients. Nairn C, Galbraith DN, Clements GB.

Regional Virus Laboratory, Ruchill Hospital, Glasgow, Scotland

When a gastric biopsy of one of the severely M.E. positive Ruchill Ottawa/Quebec patients (Pierre M) was sent for analysis to Dr John Chi in California in 2010, his tissue sample was found to be highly positive for chronic enterovirus infection.

These are slides of enterovirus positive gastric mucosa on a classical chronic, severely ill, Nightingale M.E. patient. This investigation was performed by Dr John Chia in 2010 from a Nightingale patient who fell ill in 1987.



SECTION 3

Discussion on the Insurance promoted idea, all ME & CFS patients recover within two years or sooner

In the literature there is often discussion that all CFS patients recover within a two-year period. This is an insurance promoted idea. However there is a basis for this belief.

Older patients in the 20-40 year range who fall ill with typical EBV infectious mononucleosis (Glandular Fever in the UK) are relatively easy to document. They tend to have severe illness associated with **(a)** severe caseous pharyngitis, **(b)** significant elevated temperature, **(c)** very large cervical glands, **(d)** extremely high mono-nucleosis count on blood smear resembling leukemia, **(e)** enlarged spleen, **(f)** total body severe measles like rash if treated with Ampicillin or its derivatives.

Many of these older patients die, particularly if pregnant. However we have bound one peculiarity in this group. We have been able to culture live EBV from the pharyngeal washing in those who remain seriously ill. Within one month prior to their total recovery, we have no longer been able to recover EBV from their pharyngeal wash. It is quite possible that those patients who recover totally after experiencing a severe disease state are actually EBV patients. They are not common. For all purposes, EBV patients do not occur in epidemic patients. Recovery in the majority of these patients is complete within two years or within a month of no longer having recoverable EBV from pharyngeal washings.

In 25 years, we have never been able to recover EBV from throat washings or significant mononuclear cells or seen caseous pharyngitis in any M.E. patients.

SECTION 4

Muscle Dysfunction:

Muscle testing is mentioned in the definition area, however, there are many important facets that we have not been able to discuss due to my inability to access technology in Canada. Although this is a significant complaint in almost all M.E. patients this has not been noted in this list of the 10 most common diagnostic features. The reason is simple. I have tested all of the above findings in the Canadian hospital system and found them as noted. In Ottawa and in Ontario I have no access to a physiological muscle laboratory. Dr D. R. McCluskey has demonstrated lower exercise tolerance than in sedentary subjects due to decreased aerobic work capacity. D. Halliday had demonstrated a significant reduction in muscle RNA suggestive of impaired muscle protein synthesis. David Doyle has demonstrated abnormalities in both light an electron microscopy in 30% of M.E. patients. He also found endplate anomalies in some patients. L. Archard has demonstrated persisting enteroviral infection in muscle samples from M.E. patients supplied by Dr John Richardson. This failure to include muscle dysfunction in this list is more related to my in ability to test for muscle pathology in Canada than for its absence of this as a legitimate M.E. pathology.

Caution: Also there is no indication whether these muscle dysfunction test were conducted on acute onset M.E. patients. The pathologies of acute onset M.E. patients as a group differ significantly from gradual onset patients CFS patients, whom I refer to as CFS and not as M.E. Gradual onset CFS patients tend to be misdiagnosed as M.E. and as a group have major and multiple missed organ and system pathologies rather than having typical M.E. Many CFS have no observable CNS findings.

SECTION 5

Vascular Pathology in M.E. Patients

I have spent a good time discussing the vasculitis issues of M.E. and its differential diagnosis, I have not discussed M.E. vasculitis in the technical detail it deserves although vasculitis is a common finding and probably a universal finding in M.E. patients. Vascular pathology is obvious in most moderate M.E. patients and in all severe M.E. patients.

Vasculitis is commonly associated in several major illnesses. Perhaps I should remind the reader that many believe Paralytic Anterior Poliomyelitis is a vasculitis of the capillaries supplying the anterior horn cells and Multiple Sclerosis is considered to be a vasculitis of the capillaries supplying the Schwann cells in the brain that then react by demyelination.

Dr E Ryll diagnosed an epidemic M.E. Vasculitis in the 1975 Mercy San Juan Hospital in the Sacramento, California epidemic. There, the hospital staff fell ill with an M.E. with an obvious vasculitis. This was a highly contagious epidemic that rapidly spread to staff family members. Significant disability has persisted in those affected until at least 1992 when last reported. As in many hospital epidemics, attempts have been made to suppress this epidemic information by the hospital, possibly due to insurance concerns.

There is a large scientific literature on the role of vasculitis in M.E. Up to 2008 I have counted at least 14 published papers by Dr Vance Spence at University of Dundee in Scotland concerning M.E. vascular pathology. He is just one of the researchers who have contributed to this area.

The following is a clip quoted from Dr Vance Spence that clarifies one of the pathological routes of M.E. vasculitis.

"In three separate studies, we have demonstrated abnormalities of the acetylcholine (ACh) mediated vasodilator pathway in CFS/ME patients. We found enhanced sensitivity, which was specific for ACh. This sensitivity is unusual and might be important to the underlying pathophysiology of the illness. Sensitivity to ACh was restricted to those patients within the CFS construct **Who fit descriptions for myalgic encephalomyelitis (ME)**".

(1) Spence VA, Khan K, Belch JJF. Enhanced sensitivity of the peripheral cholinergic vascular response in patients with chronic fatigue syndrome. American J of Medicine 2000; 108: 736-39 (2) • Spence VA, Kennedy G, Belch JJF, Hill A, Khan F. Low grade inflammation and arterial wave reflection in patients with chronic fatigue syndrome. Clinical Science 2008; 114: 561–566

SECTION 6

The possible role of genetic susceptability in M.E.-like patients

Ehlers Danlos Syndrome (EDS)

One of the more severe forms of acute onset vascular M.E. is Ehlers Danlos Syndrome. There is not one Ehlers Danlos Syndromes but at least 8 varieties. Some cause such severe anatomical and physiological changes that the child does not survive infancy. Probably each of the EDS variants are all genetic based illnesses although I have never seen a genetic study published on each of the subtypes. One of these EDS subtypes is important in any discussion on the subject of M.E., which I will now briefly outline.

I have only seen Ehlers Danlos in women. Their illness tends to be severe and often misdiagnosed. Whether this is a variant of M.E. only time will tell but if it is not it should be placed in this group for the moment. The patient usually falls ill sometime after the age of 16-18.

Up until this moment there is no indication of any M.E. or CFS like abnormality. It is possible they may have previously been diagnosed with hyper-reflexia or as a child they may have amused their friends by their double joint manifestations. Probably all EDS have abnormal connective tissue in their blood vessels. These patients all seem to have fallen ill immediately after an untyped infectious episode or following an immunization. I believe these women have a genetic disease and it is either turned on by a specific virus or alternatively by some aging trigger.

These hyper-reflexive EDS patients tend to be light sensitive, and suffer from severe Dysautonomia with one or more of the following: POTS (orthostatic tachycardia syndrome), IST (inappropriate sinus tachycardia, and NMH (neurally mediated hypotension).

Marfan Syndrome

Marfan syndrome in its extreme form is quite easy to recognize and is due to an inherited genetic trait of the connective tissue. The classical Marfan patient is a tall thin, thin-headed individual with long limbs hands and fingers and long narrow feet. In the extreme form the patient develops severe aortic and valvular pathology that today can be replaced where previously many of these patients died before reaching 20-30 years. These patients are easily recognized by their parents and their physicians. Wikipedia has an excellent review of the pathological findings in these extreme patients.

Our problem is not the classical easily diagnosed Marfan individual but in the wide variety of expression of this genetic illness. These milder disease forms of patients often are missed and not diagnosed as Marfan syndrome but present with a history of gradual onset fatigue syndromes and as with its close cousin, Ehlers Danlos Syndrome they should be considered in the differential diagnosis

In my patient physical examination check-list, I have a triad of progressive illnesses. Hyper-extensive syndrome, Ehlers Danlos and Marfan disease. All three are associated with fatigue syndromes and dysautanomia. The three are not related but they do form a progressive cause of the dysautanomia family of pathologies. My check-list of Marfan features is as follows:

(a):Family history Yes/No

(b) Excessive height Yes/no:

(c) Span of the arms exceeding height Yes/No 1:1

(d) Scoliosis of the spine: yes/no

(e) dilatation of the dural sac of the lumbar spine: yes/no

(f) High arched palate: yes/no

(g) Crowded Teeth: yes/no

(d) Ectopia lentis: yes/no or history of early retinal detachment or major ophthalmologic anomalies

(f) Pectus excavatum:yes/no

(g) Flat feet: Yes/no

(h) Aortic aneurysm: Yes/no

(i) Mitral valve prolapse: Yes/No

(j) Dysautanomia

(k) History of unexplained pneumothorax or sleep apnea

(l) Stretch marks on back: yes/no

SECTION 7

Bacteria pitfalls resembling an M.E. or CFS-like illness

Brucellosis

Brucellosis, once called Mediterranean Fever or Undulant Fever may have been the illness that caused Florence Nightingale to fall ill in the Crimea. Brucellosis is caused by a bacteria associated with infected animal milk and meat contact. It is a rare disease but it can cause a typical M.E. type illness. I have found only three cases,

one in Canada in a veterinarian who examined wild animals for the Provincial Government. He examined road kill. I have also diagnosed two sisters in Alabama. My father, also from Alabama had a severe fatigue syndrome and died at the age of 47 after contacting Brucellosis. He was a hunter all of his life and may have contacted the illness from wild animals. Reputedly there is no brucellosis in the USA or Canada among domestic animals.

Unlike M.E. Brucellosis has a marked elevated and undulant fever that rises and falls for weeks if left untreated. However due to the significant muscular pain and sweats it can be mistaken for M.E. unless the physician is aware that there is almost never an elevated fever in most cases of M.E. Except for the significant fever (continuous or intermittent) the other symptoms, headache, weakness, sweating, chills, arthralgia, depression, weight loss or generalized aching can resemble those of M.E.

Diagnosis is made by **(a)** blood culture but the growth will take up to 2 months, **(b)** antibody test and (c) radiological evidence in the vertebrae. **Treatment** is with antibiotics for an extended period.

Brucellosis still infects up to 100 persons per year in the USA and approximately 10 persons per year in Canada.

Lyme Disease / Borrelia burgdorferi

This is an illness that has many of the hallmarks of M.E. However for years the Canadian and Provincial Health Agencies have downplayed its very existence in Canada. It is now a recognized and increasing problem in Canada as it is in the USA.

Lyme disease is caused by a spirochete Borrelia burgdorferi carried by at least three different tic species in Canada. The tics exist across Canada and up to 15% of the tics are infected with Borrelia. The tics can be contracted by hiking and brushing against foliage. Pet animals can pick up the tic and spread it to their owners.

The initial insect bite, if it occurs and is recognized is characterized by a bull's eye rash or an erythema migrans lesion. If not treated this infection can cause chronic flu-like symptoms, painful joints headaches and fatigue. The disease can spread to the nervous system,

the heart and joints. Once spread it becomes significantly more difficult to treat. The disease can be diagnosed by PCR but there is very low to moderate sensitivity when tested in the initial stages. Many early tests are negative. Western blot is a good diagnostic tool, **IF** the bands are interpreted correctly. Therein lies a problem since the band for Lyme is almost identical to a common residual band left by a prevalent historical streptococcal infection, which has no significant associated chronic illness.

This historic denial of the health authorities to the existence of Borrelia in Canada provoked one physician, Dr Ernie Murakami in Hope, British Columbia to champion the cause of his patients, objecting to the Provincial and Federal Health Agencies negative position. This of course did not endear him to the BC Provincial Health agencies and circa 2007 his practice was investigated and his license to practice medicine in British Columbia was removed.

In February 2008, the Canadian Broadcasting ran a story of a severely disabled young woman with reputed Lyme in which the physicians advised her to get psychiatric help instead. Unfortunately this has been a common medical reaction to Lyme as it has been with M.E. and CFS. This has only been complicated by a private laboratory in California, reputedly misdiagnosing the bands on Western Blot, where reputedly they mistook a band caused by a banal past streptococcal infection as being due to Borrelia.

Since initially the diagnostic tests may be negative there is a question of whether the patient with any tick bite should not be treated with the appropriate antibiotics since waiting until the chronic illness develops may cause the patient significant and possibly permanent damage.

Only in January 2008, did the CDC acknowledge their diagnostic laboratory were insufficient and suggested the following should now be employed to confirm the diagnosis:

a. positive culture for B. burgdorferi;

b. two-tier testing (ELISA screening and

c. Western blot confirming

d. or single-tier IgG (old infection) Western blot.

Previously, the CDC only included laboratory evidence based on (a) and (b) in their surveillance case definition, refusing to do Western blot unless a & b were positive. This caused some patients to be misdiagnosed and go untreated. Today, these problems have been overcome and effective diagnostic measures are in place in Canada.

SECTION 8

Discussion Concerning Physiological Brain Mapping

M.E. is primarily a diffuse measurable vascular encephalopathy and the consequences of this encephalopathy. If this is true then one should be able to prove it by testing.

There are several excellent physiological brain mapping tools that can be used to demonstrate CNS patho-physiological abnormalities of the M.E. patient. The understanding of these tools and the interpretation of the findings are essential in the investigation of M.E. patients. **No single tool should be considered diagnostic of a disease process.** However, if several tools suggest the same pathological focus supporting the clinical picture, this can be considered to be evidence that is strong enough to be used in court, or to convince an insurance company.

A partial list of some of these tools and a discussion of these tools and their inherent difficulties follows:

1. EEG,
2. QEEG or BEAM scanner,
3. Cardiac Assessment: ECHO, Stress test, Holter Monitor testing,
4. Carotid Doppler,
5. Transcranial Doppler, (TCD)
6. X-Ray Computerized Tomography
7. Brain MRI/MRA
8. Brain SPECT
9. Sleep Studies with Holter Monitor

Discussion of problems associated with investigational tools

One should not assume that any of these tests are important in themselves. What is important is correlating different technologies to establish brain injury and this is what this discussion is about.

(1) EEG: (Electron Encephalogram) This is a complex tool and neurologists who read them tend to do so rapidly. Many in Canada tend to state the **EEG is normal if there is no seizure evidence and abnormal if they see evidence for seizure**. Rarely are more detailed reports given. At a Symposium held in Florida in 1990 an EEG was shown to some 500 neurologists. Circa 480 neurologists said it was a normal EEG. Most of 20 who said it was abnormal but were not able to say what the pathology represented. The patient had a large brain tumor. Only one of the approximately 500 neurologists diagnosed the possibility of a brain tumor. When ordering an EEG the physician should always ask the neurologist to note any lateralization of any irregularities. Often the physician will find the lateralization localization consistent with other tests.

(2) QEEG: (quantitative EEG) is termed BEAM scanner in the USA (Brain Electrical Activity Mapping): Significant difficulties are inherent in extracting clinically useful information by visual inspection from the massive amounts of data contained in any electroencephalogram or evoked potential recording. Spatiotemporal information contained in EEG recordings is significantly increased by computer-controlled topographic mapping with brain electrical activity mapping (BEAM) **(i)** tumors can be diagnosed in QEEG from patients with reputed normal EEGs so the information is there but simply not interpreted, **(ii)** other electrophysiological abnormalities can be demonstrated in patients with functional lesions but normal CT scans. **(iii)** Finally, with QEEG / BEAM, patients can be given visual, auditory or sensory information and the normal or abnormal CNS reaction can be noted in QEEG/BEAM scanning technology. The problem in Canada may be funding and criticism from neurologists. I have often wondered if neurologists have essentially banned QEEGS in Canada since computer generated EEGs can be read by a technician thus potentially depriving neurologists of significant funds. It is also

possible that the Provincial insurance agencies do not wish to pay for this technology. Fortunate those patients who have access to such a hospital with combined access to QEEG.

Note: With QEEG we have been able to demonstrate not only left posterior temporal and anterior parietal significant brain damage in a M.E. patients but in two such patients we have been able to demonstrate the brain was attempting to rebuild these injured areas in the posterior right parietal lobe. This simply could not have been found with an EEG although the information was always there.

(3) Cardiac Assessment:

The investigation of brain function requires the study of the basics. I always start with a full cardiac assessment. Sufficient M.E. patients have both anatomical heart disease that has never previously been investigated. We routinely find coronary, septal, valvular and ascending and sometimes descending aortic defects. We frequently diagnose electric or rhythm irregularities. Whether these findings are due to the disease process or not we cannot say but these physical problems may have a significant effect on CNS vascular mechanics. These are frequent findings in those patients we refer to as CFS who have normal brain function tests. These findings alone are sufficient to cause a fatigue syndrome in CFS patients. There is no evidence in any of the CDC studies suggesting psychiatric associations that such routine testing has ever been performed.

(4) Carotid Doppler:

The Carotid Doppler is well known and it is a simple and inexpensive test to demonstrate blood flow through the four arteries supplying blood to the brain. The two carotid arteries and the two vertebral supply the brain. The vertebral arteries pass through the foramen magnum and unite into the singular basilar artery. The basilar artery supplies the cerebellum, pons and brain stem.

Significant carotid and vertebral obstruction is not common in younger M.E. patients but we routinely find these pathologies in gradual onset CFS patients. Failure of this system is routinely found in older so-called CFS patients. Atheroma or plaques are routinely found in the carotid arteries or the main blood supply to the brain. Large atheroma block the blood supply to the brain causing CFS symptoms. The

presence of smaller atheroma may indicate that pieces have already broken off causing TIA's, transient ischemic attacks that may give rise to a diagnosis of CFS or anxiety neurosis. We routinely find these pathologies in gradual onset CFS patients. It is essential to first do a Carotid Doppler to understand potential vascular problems affecting the arterial system higher in the brain. Only following a Carotid Doppler can we effectively perform a Transcranial Doppler.

(5) Transcranial Doppler (TCD):

The Transcranial Doppler was invented by the Norwegian, Rune Aaslid in 1982. In 1985 he came to the University of Washington in Seattle, USA where he introduced this inexpensive technology to the USA.

TCD is an inexpensive non-invasive manner to measure the blood flow velocity of the cerebral arteries. Measurement can be made of the relative blood flow on both sides of the brain. Unlike an MRA (magnetic resonance arteriogram) it is inexpensive technology and it can also demonstrate arterial spasm by noting increased velocity in the affected side of the brain or in individual CNS arteries. This technology can thus demonstrate intracranial stenosis, collateral arteries, subarachnoid hemorrhage and diseases causing arterial spasm such a migraine. Views can be taken through the relatively thing temporal bones, the eye and the lower occiput. One must remember, the image of CNS arteries seen in MRA (Magnetic Resonance Arteriogram) are really an average of the pulsating arterial diameter. In a TCD the physician can actually see the specific brain artery pulsating. If the physician assists at this rapid technology it is possible to pick out significant pathological sites as well as being able to document the speed of the blood flow. The physician should always ask for the raw data that actually shows the individual arterial blood flow speed.

The technique has contributed to understanding cognitive, motor and sensory functions and the study of major brain functions such as language, colour and intelligence processing. You can see why this technique is important in M.E. investigation. You might wish to look at Wikipedia, Transcranial Doppler for more information in this fascinating tool.

Problems with TCD

There are at least two problems with this tool. The first is structural. It is sometimes difficult to access these "brain windows" in thick boned skulls, however in most patients there is no problem.

The big problem is not with the technology but with the bureaucrats governing access to TCD. The biggest problem in Canada is that for reasons known only to themselves, the Provincial Insurance Company, OHIP, billing code for Carotid Doppler and Transcranial Doppler is the same. If the hospital or clinic does both they are only paid for one. So since it is more difficult to perform a TCD most private clinics and provincial hospitals have simply dropped this test. M.E. is a vascular encephalopathy pathology and this non-invasive, inexpensive TCD test easily demonstrates vascular spasm. Since 2010 for all purposes it is nearly impossible to access TCD Canada. This test should be billed at a higher rate with its own code in Canada. This has simply not happened.

TCD actually gives more information than the very expensive MRA (magnetic resonance arteriography) and is essential for combining EEG, QEEG/BEAM, and SPECT technologies to demonstrate localized brain injury, which is seen in every M.E. patient.

(6) CT or CAT Technology: X-Ray Computed Tomography:

This is an expensive high cost, high radiation instrument that is of little use in M.E. patients. It is employed mainly because it exists and physicians who do not understand M.E. simply think if there is anything wrong with a patients brain they can see it on a CT scan. CT brain scan is a useless test for M.E. diagnosis. CT is much more expensive and dangerous when compared to trans-cranial Doppler. Dr David Brenner, director of Columbia University's Center for Radiological Research estimated that up to 2% of all cancers in the U.S. may be caused by radiation from CT scans

(7) MRI/MRA: Magnetic Resonance /Arteriogram Imaging:

MRI and MRA with contrast (Gadolinium) is not very useful in the investigation of M.E. patients except in the early demonstration of UBOs or Virchow-Robin spaces, but it is VERY useful if you have made the wrong diagnosis of the cause of brain dysfunction. In the early

investigation of M.E. Dr Charles Poser of Harvard recognized both **(i)** oligoclonal banding and **(ii)** increased spinal fluid pressure in M.E. patients. Increased spinal fluid pressure may be what is responsible for the large Virchow-Robin spaces seen in many M.E. patients.

However, MRI/MRA is an excellent technique to demonstrate arterial anomalies, aneurysms and if requested, a good understanding of the pituitary structures and any pathological area of the cerebella tonsils. If the physician doesn't ask for these areas they are likely not to get them and every now and again we pick up a pituitary adenoma, increasingly so in patients with thyroid pathology which is a common M.E. finding. I regularly pick up pathology using these expensive but excellent machines. Too many patients diagnosed as M.E. have had previous and unrecognized brain damage. Ventricular enlargement, flattening of sulci and tumors can be easily recognized by this technique, all of which can give rise to many M.E.-like brain dysfunctions. As in all of these technologies, it is important to not rely on a printed report but to discuss the findings with the neuro-radiologists. MRI/MRA are more difficult to read for the average physician but it can be easily learned. Reading MRI/MRA is more difficult than reading SPECT scans but sometimes radiologists miss things and a cautious question may at times be helpful. I have found radiologists some of the easiest hospital physicians to talk to. They spend a lot of time in their cubbyholes and generally like meeting the ordering physician to obtain details of the patient. Physicians should learn to read MRI and MRAs.

(8) Brain SPECT (Single Photon Emission Computed Tomography)

This is a technology that by the use of gamma ray tracers demonstrate how blood flows to the brain tissue and how brain cells metabolize this blood marked with one of various tracers. It is a less expensive technology that PET (Positron Emission Tomography) SPECT radiation level is very low, less than what one would receive in a standard chest X-Ray. Yet information is incredibly superior in a well-done brain SPECT. Radio isotopes are marked with tracers that include iodine-123 in Thyroid scans, (HMPAO):technetium-99m, (ZENON): xeno-133, Thallium: thallium-201 and flurine-18 used in PET scanners.

To my knowledge, in the USA, Canada and the UK there is at this moment only a data base for the tracer HMPAO i.e.Tc-hexamethylpropyleneamine Oxime). However most Brain SPECT

analysis in Canada are performed with other tracers without an acceptable database.

Once again there are a lot of problems with Brain SPECT Scans and almost none of the problems are with the brilliant technology.

I don't know where the greater blame lies. One of the problems in Canada is the provincial insurance companies, the hospitals and health funding problems in North America. In Canada there is a problem with the poor pay given to SPECT physicians who often are allowed to work part time in Ontario and Quebec. Perhaps it is the bureaucratic drive to cost saving and efficiency have partially destroyed reasonable access to Brain SPECT tools and technology. Nor do some neurologists seem to like this technology, possibly because of their drive to find anatomical lesions rather than physiological lesions. There is a question asked: How will this technology allow me to cure the patient? Since you cannot operate a diffuse brain injury there will be only diagnosis. However a SPECT diagnosis may help the patient obtain his disability insurance.

SPECT is a brilliant tool to interpret vascular and metabolic abnormalities and that is essentially what we are talking about in the understanding of M.E. The USA has placed an embargo on developing a data-base on normal patients, children or adults and this has caused major problems in developing data base for this technology. I was introduced to SPECT in California by Dr Jay Goldstein and Dr Ismael Mena, two of the kindest and most brilliant physicians I have ever met.

*(**Caution:** It is my understanding that in the USA, Canada and the UK there is at this moment only a data base for the tracer HMPAO i.e.Tc-hexamethylpropyleneamine Oxime). (Physicians should learn to read brain SPECTs themselves and discuss the findings with the neuroradiologist.)*

(9) Sleep Studies with Holter Monitor

This is an essential test in patients who claim to have seizures, which are not picked up on regular EEG. In a few important cases missed seizures are an important cause of severe sleep pathology.

SECTION 9

We propose that the diagnosis of Chronic Fatigue Syndrome (CFS) should be limited to gradual onset fatigue syndromes and that all of these gradual onset CFS patients should be carefully investigated for major organ or system pathology. In our experience gradual onset CFS patients tend to have significant missed pathology that may be correctable if a diagnosis is made early in their disease process. In our investigations, because CFS represent so many serious and very different disease processes, it is of limited value to take seriously any uniform viral theory of cause or any uniform treatment when referring to CFS.

SECTION 10

Reputed Psychiatric Disease in M.E. and CFS Patients: In our experience, after total body investigation of all organs and all systems, the number of patients with significant psychiatric disease findings are less than one would anticipate in the general public. Of course patients with any chronic illness, removed from their normal social life, school or work experience the problems associated with isolation and frequently of poverty. There is a bias in all research and we also have a bias. Most M.E. and CFS patients that we investigate tend to come from middle or upper middle class families, individuals who have done well in education, position and income. This general academic, athletic and financial success of our patient group undoubtedly tends to weed out many significant psychiatric illness patients.

Note: Although we discuss CFS briefly and some of its associated problems in this definitional paper, this is a definition of Myalgic Encephalomyelitis (M.E.). This is NOT a definition of CFS.

For Information concerning common missed pathologies in CFS patients please refer to:

*The Nightingale book, **Missed Diagnoses**, which can be ordered on Lulu.com and tends not to be available on Amazon.com.*

The Nightingale logo, ***"Tiger in Kew Gardens"****, was donated by the artist* ***Beryl Cook*** *thanks to* ***Jess Wilder of Portal Gallery, London****.*

One of the earliest findings in M.E. was the fact that the Natural Killer Cells were decreased in both number and activity. Natural Killer Cells are amorphos omoeba looking cells.

We felt the Tiger as a Natural Killer was a better logo.

Byron Hyde MD

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