Functional Herbal Medicines & Dietary Supplements

Taking Competitive Advantage of the Science Factor

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Chapter 1

New-Age Health Concerns and the "Science" Behind the Discussion

Chronic fatigue syndrome

In his *Report of the FNRS Contact Group, assembling the Deans of the Faculties of Medicine and the Royal Academies of Belgium*, published in October 1998 and which evaluated "Non Conventional Practices", Professor Jacques Boniver mentions chronic fatigue syndrome (CFS) as one of the three most cited reasons for patients to turn towards alternative healing methods.

Indeed, given physician scepticism about CFS and consequent antagonism between CFS patients and the traditional medical establishment, many CFS patients have dropped out of the medical care system.

Simon Wessely, the renowned British psychiatrist, wrote in 1998[1] that, when he started an NHS clinic, senior colleagues told him not to waste his time on a non-existent condition. In those years, he says, the condition was called ME (myalgic encephalomyelitis). A misnomer, because – in his eyes – there is no such thing as encephalomyelitis, "meaning inflammation of the brain and the spinal cord".

The more neutral phrase, chronic fatigue syndrome (CFS), has helped professional acceptance of the condition, experienced by an estimated 300,000 people in Britain, according to Wessely, who also notes that the Victorians recognised its existence and wrote and argued about it. He mentions that the interest declined at the start of the century, before re-emerging in the mid-1980s, helped in this "renaissance" by the consumer revolution and the rise of active and skilful support groups. "It was the time of HIV, so few could fail to grasp the significance of a mysterious virus that affected the immune system, which was how ME was then viewed", he writes.[2]

Philip Lee, M.D., confirms the view that CFS is not new. "While outbreaks of what was very likely CFS occurred in the 1930s and were studied by the US Public Health scientists in the 1950s, it was not until the past decade that substantial progress has been made in defining chronic fatigue, undertaking and expanding basic and clinical research, conducting surveillance and case controlled studies, and developing management strategies for use by clinicians in practice".[3]

In 1990, Wessely suggested that CFS has its origins in the last century, with the condition known as neurasthenia. By the late 1800s, neurasthenia was one of the most frequently diagnosed illnesses. By World War I, however, the diagnosis had almost disappeared. By the beginning of the twentieth century, medical scepticism concerning neurasthenia increased; it began to be viewed as a psychiatric disorder

[1] *New Statesman*, 30 January 1998.
[2] Professor Wessely's new book is entitled *Chronic Fatigue and its Syndromes* (Oxford University Press, ISBN 0192621815).
[3] Lee P., Recent Developments in CFS, Am.J.Med. 1998 (105) 83A.

rather than a neurological illness.[4] In addition, neurasthenia patients were increasingly held in low esteem by medical personnel. The debate that occurred about 100 years ago as to whether neurasthenia was a disease of the body or mind has reappeared with CFS.[5]

Chronic fatigue syndrome is a disabling illness that has probably afflicted humankind for centuries, although it first became prominent as a recognisable disorder in 1988, when a case definition, developed under the auspices of the US Centers for Disease Control and Prevention,[6] defined CFS as the "new onset of persistent or relapsing, debilitating fatigue ... severe enough to reduce or impair average daily activity below 50% of the patient's premorbid level for a period of at least six months".

The precise prevalence of CFS is unknown since there is no diagnostic test or pathognomonic physical finding, but it is not rare, probably being more common than Parkinson's disease or systemic lupus erythematosus.[7] CFS describes a clinical condition (i.e. a final outcome) that may develop from varying combinations of antecedent risk factors, rather than representing a single, distinct disease entity.[8]

In a review article, Wessely concluded that depression occurs in about 50% of CFS cases, with anxiety and other disorders (i.e. somatisation, minor depression, phobia or anxiety disorders) occurring in 25% of cases. These findings had their impact: some concluded that CFS is solely a psychiatric disorder.[9] For example, Abbey and Garfunkel wrote: "Chronic fatigue syndrome will meet the same fate as neurasthenia – a decline in social value as it is demonstrated that the majority of its sufferers are experiencing primary psychiatric disorders or psychophysiological reactions and that the disorder is often a culturally sanctioned form of illness behavior".[10]

From conferences and reviews in the past few years, it has become apparent that, while CFS is a heterogeneous disorder, increasing information is being accumulated on the neurologic, hormonal, immunologic dysregulation, and other biologic abnormalities that could provide clues to the pathogenesis and/or management of this puzzling illness.[11]

The most widely-accepted definition of CFS was developed for research purposes, and it is still considered developmental. The initial case definition developed by Holmes *et al.* in 1988, noted above, was replaced by a broader case definition by Fukuda *et al.* in 1994[12] but it is important to realise the weaknesses in both:

(a) they were developed based on the personal experience of a few individuals rather than on any particularly defined data set, and

(b) the criteria were established to facilitate comparison of research efforts, and therefore only a research case definition exists, not a clinical one.

New case definitions based on data from a variety of sources are currently under consideration although, for the time being, the 1994 criteria remain the "gold standard".[13]

[4] Wessely S., Old Wine in New Bottles: Neurasthenia and M.E., Psychological Medicine (20) 35-53.
[5] Friedberg F. & Jason L.A. (in press), Assessment and treatment of CFS. Washington DC; American Psych.Assn.
[6] Holmes G.P. *et al.*, Chronic Fatigue Syndrome: a working case definition, Ann.Intern.Med. 1988 (108), 387-389.
[7] Levine P.H., Recent Developments in CFS, Am.J.Med. 1998 (105) 3A (28 September).
[8] Demitrack M.A., Am.J.Med. 1998 (105) 3A.
[9] David A.S., Wessely S. & Pelosi A.J., CFS: Signs of a new approach, Br.J.Hosp.Med. 1991 (45), 158-163.
[10] Abbey *et al.*, CFS and Depression: Cause, effect, or co-variate, Reviews of infectious diseases, 1991 (13) S73-S83.
[11] Levine P.H., note 7 above.
[12] Fukuda *et al.* and the International Chronic Fatigue Syndrome Study Group, The CFS a comprehensive approach to its definition and study, Am.Intern.Med 1994 (121) 953-959.
[13] Levine P.H., note 7 above.

The international committee convened by the CDC (Centers for Disease Control) in 1993 to address the case definition[14] recognised that:

> CFS is probably the most severe end of a spectrum of fatiguing illnesses with a similar pathogenesis, including unexplained prolonged fatigue (defined as severe idiopathic fatigue of less than six months' duration) or idiopathic chronic fatigue (defined as unexplained fatigue of greater than six months' duration, but with insufficient symptoms to meet the criteria for CFS).[15]
>
> In addition, more than four of the following symptoms have to be proven present:
>
> 1. impaired memory or concentration
> 2. sore throat
> 3. tender cervical or axillary lymph nodes
> 4. muscle pain
> 5. multi-joint pain
> 6. new headaches
> 7. unrefreshing sleep
> 8. post-exercise malaise
>
> The exact determining factors for CFS are unknown, but considerable attention has been devoted to investigating a variety of precipitating factors.

Infections are common prior to the onset of symptoms, as are stressful events, and a possible explanation linking these two factors is under discussion.[16] Among other mechanisms under consideration are more endocrinologic approaches, as suggested by Bruno *et al.*, who have investigated post-polio syndrome, a well-documented post-viral illness characterised by severe prolonged fatigue and fatiguability, cognitive dysfunction, and abnormal endocrine function as a model for CFS.[17]

For Ronald Glaser, Ph.D, chronic fatigue syndrome is a condition in which the prevalent clinical symptoms are severe fatigue, myalgia, lymphadenopathy, sore throat, stress, and depression. "Because symptoms associated with CFS are often found associated with an active virus infection, studies have focused on the hypothesis that CFS is induced by a virus. For example, Jones *et al.* and Strauss *et al.* provided evidence that Epstein-Barr virus (EBV) was the etiologic agent for a chronic illness that has now come to be called CFS", Glaser writes. He continues by stating that these early studies, which contributed to the reintroduction of the concept of this illness to the general medical community, "showed that the patients with these symptoms had significantly higher antibody titers to EBV. Holmes *et al.* also found higher EBV antibody titers in patients presumed to have CFS; antibody titers to other herpes viruses such as cytomegalovirus (CMV), herpes simplex virus (HSV), and measles virus were also observed in these patients. Buchwald *et al.* and Hellinger *et al.* also found a relation between higher EBV antibody titers and CFS. Human herpes virus 6 (HHV-6) has also been associated with CFS. Higher antibody titers to HHV-6 in CFS patients are consistent with reactivation of the latent virus, the presence of IgM antibodies to HHV-6 in a significant number of patients diagnosed with CFS would indicate a primary infection."

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[14] Fukuda *et al.* and the International Chronic Fatigue Syndrome Study Group, note 12 above.
[15] Levine P.H., note 7 above.
[16] Glaser *et al.*, Stress-associated immune modulation: relevance to viral infections and CFS, Am.J.Med. 1998 (105) 3A: 35S-42S.
[17] Bruno *et al.*, Parallels between post-polio fatigue and CFS: a common pathophysiology, Am.J.Med. 1998 (105) 3A: 66S-73S.

However, he says, "over time, the association between EBV, HHV-6, other herpes viruses and CFS has not produced a consensus on the etiology of CFS. In fact, in a recent study by Buchwald *et al.*, antibody titers to 13 different viruses were measured in CFS patients; no relation was found between antibody titers to any of the 13 viruses, including latent herpes viruses, and CFS. The conclusion of these and other studies is that, whereas the clinical evidence supports the hypothesis that CFS is caused by a virus, there are no clear data that link any particular virus(es) to CFS. Interestingly, individuals who are EBV seronegative have also been diagnosed as having CFS." Glaser notes that it is now well established that the central nervous system, the endocrine system and the immune systems interact with each other. The interactions are complex.

The term "syndrome" itself covers a broad range of symptoms and perhaps a varied etiology as well. Whenever a disease is described as being a "syndrome", the means of diagnosis and, above all, the possibilities to treat the disease become all the more difficult.

Fatigue, as a subjective symptom, is one of the most common in the general community, in primary care and in tertiary referral practice.[18] According to Hickie *et al.*, syndromal diagnoses associated with prolonged fatigue – including chronic fatigue syndrome, fibromyalgia and neurasthenia – are prevalent and are major sources of health care utilisation.[19] After setting aside the essentially rare neuro-muscular diseases that cause chronic fatigue, it is clear that this ubiquitous symptom is not the result of a failure of force generation from the muscle.[20]

Currently, documentation of the prevalence and associations of chronic fatigue relies on self-report data, despite concerted efforts spanning almost a century to develop objective tests to record and evaluate this widespread fatigue.[21]

The diagnosis of CFS is made difficult by the absence of specific biomedical markers, and depends primarily on determining whether the subjective information provided by the patient meets the clinical case definition of this syndrome.[22] A natural consequence of the difficult diagnostic boundaries is overlap with other similar syndromal disorders, notably those that share fatigue as a major symptom. The list of such conditions includes IBS (irritable bowel syndrome), neurasthenia, sick building syndrome, multiple chemical sensitivity syndrome, as well as degressive and anxiety disorders.

Lloyd Andrew states that the relation of the CF syndrome to the syndrome of major depression is also paramount. Neuropsychological complaints such as concentration difficulties, memory impairment, sleep disruption and mood disturbance are almost universal in patients with chronic fatigue syndrome, and concurrent psychiatric diagnoses (predominantly depression or anxiety) can be made in a substantial proportion of cases.[23]

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[18] Lewis *et al.*, The epidemiology of fatigue: more questions than answers, J.Epidemiol & Community Health 1992 (46) 92-97.

[19] Hickie I. *et al.*, Reviving the diagnosis of neurasthenia, Psychol.Med. 1997 (27) 989-994.

[20] Lloyd A.R. *et al.*, Muscle endurance, twitch properties, voluntary activiation and perceived exertion in normal subjects and patients with CFS, Brain 1991 (114) 85-98.

[21] Muscio B., Is a fatigue test possible? Br.J.Psychol. 1991 (12) 31-46; Lloyd A.R. *et al.*, Recent developments in CFS, Am.J.Med. 1998 (105) 3A.

[22] Lange G. *et al.*, Am.J.Med. 1998 (105) 3A.

[23] Taerk GS *et al.*, Depression in patients with neuromyasthenia – benign myalgic encephalomyelitis, Int.J.Psychiat.Med. 1987 (17) 49-56; Kruesi M.J.P. *et al.*, Psychiatric diagnoses in patients who have CFS, J.Clin.Psych. 1989 (50) 53-56; Hickie *et al.*, The psychiatric status of patients with CFS, Br.J.Psych. 1990 (156) 534-540.

The potential role of infectious agents in producing chronic fatigue has been a strongly-favoured hypothesis. This notion arose naturally from the historical observations linking specific infections such as brucellosis to a subsequent fatigue state. Further support for this possibility comes from the anecdotal histories of patients with chronic fatigue syndrome and the attributions made to prior events by physicians. These recollections typically describe a "flu-like" illness demarcating the patient's prior good health from the subsequent chronic fatigue state. Unfortunately, these associations are frequently retrospective attributions with uncertain validity (as the expected incidence of symptomatic viral infections in the general population is approximately four annually), making chance associations likely. Many of the patient groups reported to date are also confounded by the selection bias of referral to specialty clinics because of the history of an infective illness.[24]

According to Levy *et al.*, because the illness often begins with flu-like symptoms in a previously well person, one hypothesis is that the illness is caused by immune abnormalities – perhaps triggered by some infectious agent.[25]

According to Benjamin H. Natelson *et al.*, several reports have suggested that immune dysfunction can be an important component of CFS. Early reports focused on clinically available serum tests, including circulating immune complexes (i.e. Raji cell and C1q binding) and immunoglobulins (Ig) A,E,G and M, and IgG subclasses. More recent work has examined lymphocyte cell surface markers thought to represent immune activation and noted that cell types bearing these markers exist in increased numbers in patients with CFS relative to healthy controls. Finally, some reports indicate low numbers of natural killer cells in CFS. The reports on immune abnormalities in this illness apparently justified patients – and even some physicians – coining the term "chronic fatigue immune dysfunction syndrome".[26]

When the syndrome has multiple origins, how should it be treated? In the case of supplementation and natural products, what products could be of help?

Nutrition science is rather poor in this field. However, that offers an opportunity to those companies willing to invest in necessary research in this field.

One company that has started a serious examination of the possible health benefits of specific nutrients is Advanced Plant Pharmaceuticals Inc. (APPI), which launched a standardised pharmaceutical grade nutritional product – a nutritional version of abaca – called ACA. The company says that its product has been proven to strengthen the immune system as well as fight the spread of HIV virus. ACA is an orally-ingested compound that in pilot studies, case studies and *in vitro* studies in the US and other countries has demonstrated reversal of glandular swelling, restoration of well-being and associated weight gain, improvement in response to skin hypersensitivity tests and an increase in the circulating concentration of helper T cells (CD4-positive cells). Associated with this is an improvement, in the CD4/CD8 ratio, with many patients returning to a normal ratio. This type of response is far different from those experienced by users of any drug regimen currently on the market, according to the company. People who have access to the expensive new class of drugs called protease inhibitors have seen similar responses when used in combination with AZT or one of the older products, but they are not effective for all people.

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[24] Lloyd A.R. *et al.*, Recent developments in CFS, note 21 above.
[25] Levy *et al.*, CFS: is it a state of chronic immune activation against an infectious disease? In: Root R.K.,Sande M.M.A. (eds), *Viral infections: diagnosis, treatment and prevention*. New York: Churchill Livingstone 1992, 127-144.
[26] Natelson B.H. *et al.*, Recent developments in CFS, Am.J.Med. 1998 (105) 3A9.

The struggle for appropriate medication is all the more difficult because scientists and physicians do not have a clear understanding of which drugs work best together and whether a patient will prove to be resistant to any of the drugs in the combination therapy now in use.

Another company working in this field is BASF, which promotes its SAMe product for several indications, including CFS (for more information on SAMe, see further in this report).

According to the Centers for Disease Control, over 14mn people in the US experience chronic fatigue symptoms. APPI estimates the CFS and immune markets to be in excess of $6bn.

• Enada relieves symptoms of CFS (using strict FDA testing guidelines)

In February 1999, Menuco Corporation announced that Enada, a natural energy-enhancing nutritional supplement – tested by researchers at Georgetown University Medical Center, Washington DC – had achieved significant improvement in relieving the symptoms of people suffering from chronic fatigue syndrome (CFS). Although the Georgetown trials focused on people diagnosed with CFS, Enada is also a nutritional supplement for healthy individuals who desire additional energy; it is one of the first nutritional supplements to be tested using strict FDA guidelines to determine its safety and effectiveness. In 1996, the product received an Investigative New Drug (IND) acceptance from the FDA allowing it to begin a human double-blind, placebo-controlled, cross-over study following strict pharmaceutical and drug testing guidelines.[27]

Georgetown doctors found that 31% of the patients who took Enada achieved significant improvement in the relief of their symptoms. In a follow-up study, 72% of the patients achieved positive results over a longer period of time. The double-blind, placebo-controlled human clinical trial results have been published in the medical peer-review journal, *Annals of Allergy, Asthma and Immunology*.

"Eighty per cent of Americans state that fatigue is their number one health complaint. We want to demonstrate through sound scientific studies, not marketing hype, that Enada is both safe and effective in providing energy enhancement to alleviate the symptoms of CFS, a debilitating disorder which affects half a million Americans," said Matt Fitzsimmons, President, Menuco Corporation. "Dr Bellanti and his research colleagues at Georgetown University Medical Center have successfully demonstrated Enada's effectiveness in increasing energy," says Fitzsimmons.

Enada is the brand name for stabilised, absorbable NADH (nicotinamide adenine dinucleotide plus high-energy hydrogen). It is the only patented, stabilised, absorbable, oral form of NADH currently on the market. For years, research scientists have known that NADH, a natural co-enzyme, plays an important role in the body's cellular energy-producing function. NADH occurs in the muscle tissue of fish, poultry and cattle – key food sources in the human diet. However, the human body absorbs minuscule amounts of NADH ingested from food sources. Also it is known that the more NADH a cell has, the more energy it can produce; therefore, the more energy a person has, Menuco says.

Georgetown researchers are planning a large scale chronic fatigue syndrome study using Enada to explore further its effectiveness for CFS. In addition, they are conducting an FDA-approved clinical trial – under the direction of the department of neurology at Georgetown University Medical Center – to test Enada's ability to prevent the mental deterioration, memory lapses, and concentration difficulties

[27] IND No.49,635; the original working name of this stabilised, patented, oral NADH product was Birmadil.

associated with Alzheimer's disease. The product has shown promise in Europe when used for patients with Alzheimer's and Parkinson's diseases.

Birkmayer Laboratories in Vienna, Austria and Menuco Corporation sponsored the CFS study using Enada. Georg Birkmayer, M.D., Ph.D., world-renowned biochemical researcher and director of the Birkmayer Institute for Parkinson Therapy, developed the first stabilised, absorbable oral NADH supplement, a result of a decade of research. He is also the first to use NADH therapeutically to stimulate the body to produce naturally the key brain chemicals responsible for energy production and muscle co-ordination. Enada is manufactured and packaged by Menuco through a licensing agreement with Merck Pharmaceuticals in Austria (Merck KGaA).

■ Preventing macular degeneration

A leading supplier of lutein is Kemin Foods of Des Moines, Iowa. The company markets its product under the FloraGLO brand name. And one of the newer carotenoid antioxidants in BASF's pipeline is lutein.

Lutein [Latin: *luteum* = egg yolk, from *luteus* = yellow] is a yellow pigment in the chemical family of carotenoids found in vegetables, marigold flowers, alfalfa, egg yolk and, to a lesser degree, in many other plants. The original medical association of lutein was as an isolate from the corpus luteum, a part of the ovaries, and hence its name.

Lutein is a class of light-absorbing chemical pigments that serve as precursors to vitamin A. The chemical name for vitamin A and its family are "retinol" and "retinoids", which express their relationship to the retina of the eye. Lutein is one of two primary pigments found in the central part of the retina (the other being zeaxanthin), which help to filter out damaging light. Lutein's antioxidant property may help protect the outer retina, which is rich in polyunsaturated fats, from light-induced free radicals.

Scientists are establishing a strong link between lutein and reduced occurrence of age-related macular degeneration (AMD), a leading cause of blindness. This dietary link to eye disease has enormous implications – and the potential to change the entire approach to eye health.

A total of 30mn Europeans and Americans currently suffer from AMD, an eye disease that accounts for one-third of the 2mn new cases of blindness in the US and the EU each year.

Early diagnosis of age-related macular degeneration is essential to successful treatment. As the name implies, the condition affects the macula, a small portion of the retina – the light-sensing nerve tissue that lines the inside of the eye. All parts of the retina contribute to sight, but only the macula can provide the sharp, straight-ahead vision that is needed for driving and reading small print.

As a person ages, changes may occur in the macula which can cause difficulties in reading and other tasks requiring good central vision. Scientists do not know why these macular changes occur, but ageing evidently plays a major role in the process. Although AMD is a leading cause of visual loss, the majority of people with the condition continue to have almost normal vision throughout their lives. Even those who are severely affected retain enough sight to move about independently and make use of helpful devices such as low-vision aids.