

Chronic Fatigue Syndrome: A look at physiological processes and therapeutics

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History

Chronic fatigue syndrome (CFS), known in Europe as myalgic encephalomyelitis, appears to have been a health issue for at least two centuries. In the 19th century, Dr. George Beard used the term neurasthenia to label a condition resembling CFS. In the 1930s through the 1950s, conditions marked by prolonged fatigue were noted in the United States as well as other countries (Schafer, 2002). From the 1970s after an influenza ridden winter in Incline Village, Nevada, Drs. Paul Cheney and Daniel Peterson observed a cluster of patients who suffered from unrelenting fatigue and were unable to recover (Peterson et al., 1986). Their interest in these patients brought renewed attention to the condition, which was originally thought to be a communicable disease with a viral related etiology. This later proved to be incorrect and the condition became known as CFS.

Defining CFS

CFS is classified as a syndrome, not a disease. Its most notable symptom is unrelenting fatigue. Being a diagnosis of exclusion, other illnesses that could account for the fatigue are first ruled out. There are no tests that will definitively diagnose CFS. The Centers for Disease Control, in a Prevention Case Definition published in 1994, described eight symptoms related to CFS. The patient with CFS will suffer from four of the eight symptoms listed in Table 1. The symptoms must have persisted or recurred during six or more consecutive months of illness, and must not have predated the fatigue. However, many people who appear to have this unrelenting fatigue often cannot be diagnosed with CFS according to the CDC definition.

While depressive patients commonly cope with

Table 1: CFS Symptoms

from Fukuda, 1994 and CDC, 2004

Severe chronic fatigue of at least six months Concurrently with four of more of the following symptoms
Substantial impairment in short-term memory or concentration
Sore throat
Tender lymph nodes
Muscle pain
Multi-joint pain without swelling or redness
Headaches of a new type, pattern or severity
Unrefreshing sleep
Post-exertional malaise lasting more than 24 hours
Other commonly observed symptoms
Abdominal pain, bloating
Alcohol intolerance
Chest pain, chronic cough
Diarrhea, dry eyes or mouth
Earaches, irreg heartbeat, jaw pain
Morning stiffness, nausea, night sweats
Depression, irritability, anxiety, panic attacks
Shortness of breath, skin sensations
Tingling sensations, and weight loss

fatigue, a depressed person will often improve with physical activity and exertion, while a CFS person normally worsens with physical activity. A study by White *et al* (2001) compared fatigue syndromes with mood disorders, comparing them with post-mononucleosis infection outcomes. They found that mononucleosis patients, although their blood cell counts were in normal range, may have significant fatigue for

months. Another unique response that sets patients with CFS apart from those with other fatiguing illnesses is that rest does not alleviate the fatigue. Without a doubt, CFS patients have great difficulty dealing with daily activity. Patients report decreased quality of life, sense of well-being, and libido. Duration of three to five years for such symptoms is common (Hardt et al., 2001).

Because many of the symptoms are subjective and cannot be observed or confirmed by a physician, the condition is referred to as medically unexplained or “functional”. Unfortunately many physicians use the term functional to mean psychosomatic, as in imagined. However, the rapidly expanding field of psychoneuroimmunology suggests that disease processes that don't involve both the mind and the body are the exception.

Although considered controversial, there is a grouping of conditions called *Functional Somatic Syndromes* (Colby, 1999; Goudsmit and Shepherd, 1999; Wessely et al., 1999). These disorders are called functional because the medical specialty labeling the condition is unable to find aberrant biochemical processes (although improved laboratory technology is changing this).

When examining CFS, a single patient may exhibit signs and symptoms of fibromyalgia (FM), tension headaches, multiple chemical sensitivity, food allergy and irritable bowel syndrome. Revisiting Hans Selye's (1976) description of the General Adaptation Syndrome and the more modern model of allostasis developed by McEwen

(2003) and Schulkin (2003), we are reminded that an environmental trigger may result in a reorganization of physiology inducing a number of systemic effects.

Chaudhuri *et al* (2003) points out that the complex of symptoms that include immunological shifts, metabolic disruption, neurological changes and endocrine modifications that occur with Functional Somatic Syndromes, are expressed in a manner that is unique to the individual. This suggest the hypothesis that fibromyalgia, chronic fatigue syndrome, migraines, irritable bowel syndrome, atypical facial pain and premenstrual dysphoric syndrome, may be more similar than dissimilar and may share some particular etiologic “step” (Gruber et al., 1996; Wessely et al., 1999).

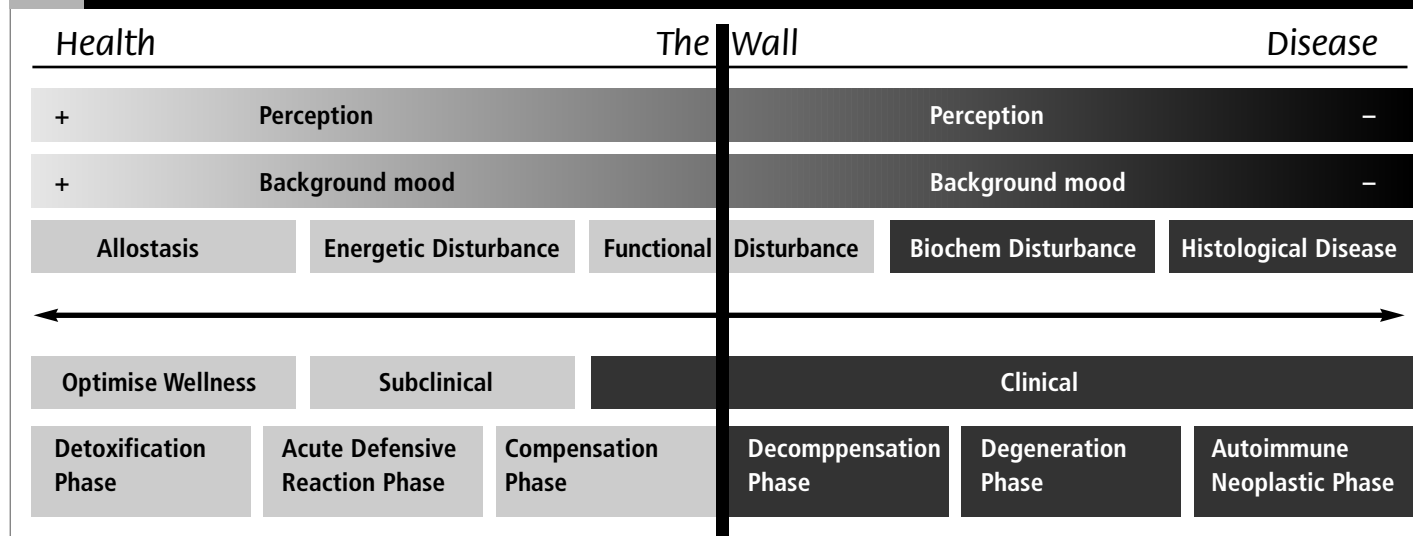
Theories of etiology

The etiology of chronic fatigue syndrome is obscure and controversial, leading to considerable obstacles to both clear diagnosis and to effective treatment. To make these conditions even more difficult to understand, it appears that CFS is triggered from a number of causes, such as infection, exposure to toxic chemicals, and psychosocial stressors (Gupta, 2002; Vojdani and Lapp, 1999). Whatever the initial insult, an upregulation of the coping response persists, which becomes a pathophysiological repeating loop (Gupta, 2002). Recent evidence suggests that neurological and psychological factors, as well as endocrine and immune factors are key in functional somatic syndromes (Gupta, 2002; Sharpe and Carson, 2001; Vojdani and Lapp, 1999; Wessely et al., 1999). Neurotransmitter alterations, as well as metabolic shifts in the brain occur in patients with CFS (Chaudhuri et al., 2003; Naschitz et al., 2002). Additionally, these patients appear to have diffuse cerebral perfusion, suggesting a rationale behind the decline in cognitive function, sleep quality, and energy levels often seen with the condition (Schmaling et al., 2003).

A possible key neurological process in this initial stage may involve the amygdala. The amygdala (and the bed nucleus of the stria terminus) are involved in primal emotions such as fear and anxiety (Sapolsky, 2003). Gupta (2002) suggests a conditioned network created in the amygdala due to habituation to chronic signals arising from the viscera. Further support for this is shown by Vyass *et al* (2002) in demonstrating impairment of long-term potentiation of the

Table 2: Functional Somatic Syndromes
from Wessely *et al*, 1999

Specialty	Syndrome
Gastroenterology	IBS
	Non-ulcer dyspepsia
Gynecology	PMS
	Chronic pelvic pain
Rheumatology	Fibromyalgia
Cardiology	Atypical or non-cardiac chest pain
Respiratory medicine	Hyperventilation syndrome
Infectious disease	CFS
Neurology	Tension headache
Allergy	Multiple chemical sensitivity
Dentistry	TMF dysfunction
	Atypical facial pain

Figure 1: Health as a ContinuumSpelman K. 2004. Allostasis: stability through change. *Austral J Med Herb* 16(4):99-109

hippocampus, while facilitating long-term potentiation in the amygdala under such conditions.

Vyass *et al* (2003) also demonstrate the extension of neuronal dendrites to the amygdala and bed nucleus of the stria terminalis under CFS-like conditions while the hippocampal dendrites atrophy. Aberrant signalling from the viscera can be involved in the induction of primal emotions and if continued can create a positive feedback between the viscera and the limbic system that becomes increasing difficult to inhibit.

Hypothalamus-Pituitary-Adrenal axis alteration appears to be a common theme between many of the Functional Somatic Syndromes such as CFS, FM, and Multiple Chemical Sensitivity (Komaroff and Buchwald, 1998; Racciati *et al.*, 2001). HPA alterations also affect the immune function (Komaroff and Buchwald, 1998). The “alarm” cytokines, thought of as proinflammatory, are elevated in CFS patients and this seems to continue for years (Torpy *et al.*, 2000).

The allostasis model of disease progression illustrates the process of physiological dysregulation (Figure 1). There are a variety of differing causes that initiate syndromes, and possibly another set of factors that enable disease patterns. A single insult such as influenza, psychological trauma, or toxic exposure, although possibly minor, combined with many other variables such as life stressors, eating habits, environmental exposures, and genomic makeup could combine to create a burden on the system.

The suggestion has been made that CFS is related to altered mitochondrial function. Energy dynamics drive nutrient transport into the cell and the transport of waste products out of the cell. ATP comes from the mitochondrial process of oxidative phosphorylation. Perhaps many of the fatigue syndromes we see are a consequence of changing dynamics of the energy gradients, or the so-called redox potential (reduction/oxidation potential) within cells (Bland, 2003). Proinflammatory cytokines (IL-1, IL-6, TNF- α , and IFN- γ) appear to be upregulated in many cases of CFS. In turn this induces nitric oxide (NO) and superoxide release from macrophages. The combination of NO and superoxide rapidly reacts yielding peroxynitrite. If this becomes a positive feedback loop, it may result in cellular damage and ultimately alter mitochondrial dynamics.

Treatment

CFS has a multifactorial etiology and any one therapeutic molecule is unlikely to effectively treat the syndrome. CFS therapy is best tailored to the individual patient (Afari and Buchwald, 2003). With the possibility of over ten million genomic single nucleotide polymorphisms (SNPs) (Gabriel *et al.*, 2002), a sensible conclusion is that there is no “average patient.” Nevertheless, a central therapeutic theme for CFS would focus on reducing the oxidative “load” on the system.

Table 3: Prognostic Predictors

from Schmalig et al. 2003, n = 100, 18 mo study

Patient Characteristics Associated with Improvement of Symptoms	Patient Characteristics Associated with Worsening of Symptoms
Better mental health	Less education
Less use of sedating medications	Unemployed
Fewer somatic attributions	Worse mental health
	More use of sedating and antidepressant medications
	More somatic attributions
	Older age
	Current depression
	More somatic attributions

Decreasing exposure to oxidative triggers and enhancing the antioxidant capacity is an obvious clinical strategy. These two steps alone may enhance cellular and mitochondrial function and therefore improve production of ATP and cellular nutrition. Other steps might include modulation of the hypothalamus–pituitary–adrenal axis, quieting excessive sensory and immunologic stimulation of the CNS, and stimulating hepatic detoxification.

This suggests a pharmacological approach using multiple agents (Pall, 2000). Many CFS sufferers, however, rely on phytotherapeutic modalities as conventional medicine has little to offer.

Phytotherapy

An evolutionary view would suggest that therapeutics using one compound to effect change in mammalian physiology is naive. Instead, evolutionary history supports a more intricate notion – exposure to phytochemical matrices. The multi-component nature of medicinal plants and formulations of medicinal plants mimics what our ancestor's genomes experienced regularly as they foraged for foods. The exposure to one chemical at a time, in an evolutionary time scale, is completely novel to biology: For over 200 million years of evolving mammalian physiology, medicinal, and food plants, have always been multi-component mixtures of nutrients and other metabolites.

Furthermore, a polyvalent mode of activity is common in the interface of phytochemistry with human systems. Messina *et al.* (2001) point out that the allelochemicals (protective phytochemicals) of plants can

have complementary and overlapping activities such as the alteration of biotransformation enzyme activities, anti-inflammatory effects, stimulation of the immune system, reduction of platelet aggregation, modulation of cholesterol synthesis and hormone metabolism, reduction of blood pressure, and antimicrobial effects.

Moreover, a number of researchers have proposed that multi-component pharmacological agents that hit multiple targets, impact the complex equilibrium of whole cellular networks more favorably than drugs that act on a single target (Ágoston et al., 2005; Briskin, 2000; Csermely, 2004; Csermely et al., 2005; Keith et al., 2005; Keith and Zimmermann, 2004; Werner, 2003). Keith and Zimmerman (2004) suggest that many genes might need complementary action to modify disease processes. In other words, efficacious therapy might depend on perturbing more than one target. Additionally, multi-target agents need affect their targets only partially, which corresponds well with the presumed low-affinity interactions of medicinal plants (Ágoston et al., 2005; Csermely, 2004; Csermely et al., 2005; Keith et al., 2005; Keith and Zimmermann, 2004; Spelman, 2005; Spelman et al., 2006). The partial “perturbations” of medicinal plants on a pharmacological network mimic accurately physiological scenarios where hundreds of different enzyme systems and receptor types and subtypes are triggered simultaneously (Ágoston et al., 2005; Spelman, 2005; Spelman et al., 2006; Spelman et al., 2006). This is compared to the complete elimination of a single network node (e.g. enzyme or receptor system), which is a rather unusual phenomenon not typically found in a physiological scenario (Ágoston et al., 2005). Thus, it seems obvious, to at least this author, that medicinal plants are quite sensible at dealing with the complexity of human physiology, whether it involves neuroendocrine processes, detoxification processes, or immunological factors.

Due to the dysregulation of immune function, immunomodulators as a class of therapeutic agents are indicated. The botanical immunomodulators may be defined as herbs that through the dynamical regulation of informational molecules (cytokines, hormones, neurotransmitters, other peptides etc.) alter the activities of the immune system (Spelman et al., 2006). Modulation of the cytokines, specifically interleukin (IL) -1, IL-2, IL-6, TNF- α and IFN do demonstrate effects



Astragalus membranaceus (astragalus)

on the HPA axis (McCance, 2001). It follows that specific immunomodulators have the potential to alter the stress axis. Additionally, many of the cytokines affect the brain, inducing behavioral effects (Kronfol & Remick 2000). This may be why this category of herbs is used in such diverse conditions and suggests further understanding of these herbs is yet to come. In any case, with their ability to modulate cytokine expression and very likely other messenger molecules, this category is particularly useful in managing the allostatic load represented by CFS. This could quiet the overexpression of proinflammatory cytokines and result in a

downregulation of the immunological portion of the repeating cycle seen in CFS. But this alone may not shift the repetitive attempts at adaptation that CFS represents. Other systems may need to be addressed directly.

The endocrine system can be addressed through the addition of the adaptogens. Downregulation of the HPA axis is commonly found in CFS. Adaptogens have demonstrated regulatory effects on energy pathways in addition to modulation of the biosynthesis of nucleic acids, the biosynthesis of proteins, the limitation of catecholamine overproduction, and the reduction of lipid peroxidation (Panossian et al., 1999). In other

Table 4: Phytotherapeutic Approach

Adaptogens, Endocrine Strategies	Immunomodulators, Immunological Strategies	Nervines, Neurological Strategies	Hepatics, Detoxification Strategies
<i>Aralia spp.</i>	<i>Astragalus mem.</i>	<i>Avena sativa</i>	<i>Arctium lappa</i>
<i>Bupleurem</i>	<i>Cordyceps cicadae</i>	<i>Bacopa monniera</i>	<i>Berberis spp.</i>
<i>Eleutherococcus s.</i>	<i>Coriolus versicolor</i>	<i>Ginkgo biloba</i>	<i>Chelidonium maj.</i>
<i>Emblca officinalis</i>	<i>Echinacea spp.</i>	<i>Hypericum spp</i>	<i>Chionanthus virg.</i>
<i>Panax spp.</i>	<i>Ganoderma spp.</i>	<i>Leonorus cardia.</i>	<i>Curcuma longa</i>
<i>Schisandra chinensis</i>	<i>Grifola frondosa</i>	<i>Lobelia inflata</i>	<i>Cynara scolymus</i>
<i>Scutellaria baical.</i>	<i>Lentinula edodes</i>	<i>Melissa officinalis</i>	<i>Iris versicolor</i>
<i>Serenoa repens</i>	<i>Picrorhiza kurroa</i>	<i>Passiflora incarnata</i>	<i>Silybum mari.</i>
<i>Smilax officinalis</i>	<i>Tinospora cordifol.</i>	<i>Piper methysticum</i>	<i>Taraxacum officin.</i>
<i>Withania somnifera</i>		<i>Scutellaria laterifl.</i>	<i>Verbena officinalis</i>



Eleutherococcus senticosus (eleuthero)



Schisandra chinensis (schisandra)

words, adaptogens demonstrate modulation of the physiological “switch on” and “switch off” systems of multiple body systems. Through the stress axis, the extracellular signaling system and the intracellular signaling systems, adaptogens have demonstrated profound effects on human health (Panossian et al., 1999). Additionally, there is research, although scant, to support some of the better known adaptogens in improving CFS (Baschetti, 1995; Ogawa et al., 1992; See et al., 1997; Singh et al., 2002B). Additionally, there is a significant volume of accumulated case studies of phytotherapists successfully dealing with CFS with adaptogens as a part of a treatment plan.

Adaptogens are often associated with plants rich in phytosterols such as protodioscin. Interestingly, Adimoelja (2000) claims that protodioscin, found in many plants, is biologically converted to DHEA. Although the author is skeptical of this claim, if this proves to be true it offers a much clearer understanding of some of the processes through which adaptogens work.

Nervines in some patients may also be key to support the neurological dysregulation of CFS. As mentioned above, the amygdala appears to play a key role in CFS. Amygdaloid upregulation perpetuates a physiology of withdrawal from the environment due to the unconscious perception of threaten. This darkens the perceptive lens that a CFS patient uses to evaluate their world. Although there is a lack of research to support this statement, nervines likely offer downregulation of the amygdaloid response. The kavapyrones and lobeline

both demonstrate modulation of amygdaloid activity in various models (Jussofie et al., 1991; Sopranzi et al., 1991). Many of these herbs do offer down regulation of the catecholamine systems (Butterweck, 2003; Leung and Xue, 2003; Schule et al., 2001). Catecholamines, both peripheral and central, influence the readiness to perceive events as alarming. Since bodily events influence the perception of a threat such as changes in heart rate, blood pressure, respiration and facial muscles (LeDoux, 1996) many of the anxiolytics through their direct sedation of many of the arousal body systems may help in altering perception of threat to one of safety.

The gut should also be addressed as it has a relationship with multiple systems in the body. In the



Ginkgo biloba (ginkgo)

authors opinion the gut is best viewed as an immunoendocrine organ influencing messaging to the other organs and body systems. The removal of dietary antigens is an obvious necessity to reduce further oxidative stress, immunological activation and excitatory signaling to the CNS. Repairing damage to the mucoepithelium will improve mucoepithelial detoxification and the symptoms of CFS (Bland, 2000; Rigden, 1998). Hepatics could also support detoxification in the gut and liver. Improving hepatic elimination, downregulating Kupffer cell activity, and decreasing the proinflammatory cytokine load can all make improvements in CFS (Bland, 2000; Rigden, 1998).

There are potentially hundreds of options when it comes to phytotherapy. The above herbs listed in Table 4 are merely a short list of possible options. A sensible strategy is the use of botanicals from various categories of actions. Choosing herbs that modulate the function of the immune system, the endocrine system, the CNS, and hepatic detoxification drawn from adaptogens, immunomodulators, nervines, and hepatics may offer the best clinical strategy. Secondary categories may include the lymphagogues for further assistance in improving immune function through the reticuloendothelial system. Gut demulcents and astringents for protection and repair of the gut wall could greatly aid this process. Repairing damage to the mucoepithelium has the potential of enhancing immune function (Bland, 2000; Rigden, 1998).

What the author's clinical experience suggests is no one plant or one protocol is going to work for improving CFS or the wider rubric of Functional Somatic Syndromes. These patients come with layers of complexity that the clinician must consider. Paying attention to the patient and their psychosocial and environmental context will give the clinician the best clinical signs to guide protocols, which plants and lifestyle suggestions to make first and provide for the best chance at invoking a response. Above all, it should be understood that a CFS patient has a different physiological and psychological response to the environment due to the complexity of their syndrome. Since environmental context is so key in amygdaloid response and health in general, serious consideration must be given to inspiring the patient to create a healing environment. Thus this necessitates care that is

individualized to the patient. Following a one formula treats all CFS patients approach is unwise.

Nutritional factors in CFS

It should be remembered that CFS patients often don't have the will to eat and are therefore, quite likely subclinically deficient, if not obviously deficient in a number of nutrients. Therefore dietary counseling can be of considerable benefit. Dietary modification has demonstrated improvement in the signs and symptoms of Functional Somatic Syndromes (Logan, 2003; Nicholson, 2003; Rigden et al., 1998). Logan (2003) suggests the elimination of dietary excitotoxins (eg MSG), decreasing the inflammatory milieu, building positive colonic flora, decreasing microglial activation, and reducing oxidative stress. Others have shown success with improving GI and hepatic detoxification and mitochondrial resuscitation by the use of



Iris versicolor (blue flag)

Table 5: Researched Nutritional & Supplement Strategies in CFS

Diet	Antioxidants	Hormonal	Other
↓ Ag exposure	NAC	Melatonin	ω-3 / EFAs
↑ Antioxidants	Tocopherols	DHEA	Mg ⁺⁺
↑ "color" in diet	CoQ10	Human Growth Hormone	N-acetyl carnitine
↓ processed foods	a-Lipoate		B complex
↑ protein	Vitamin C		
	Quercitin		

antioxidants (Nicholson, 2003; Rigden et al., 1998). Antioxidants such as N-acetylcarnitine, tocopherols, coenzyme Q10, lipoic acid, melatonin and vitamin C have demonstrated efficacy (Lister, 2002; Kodama et al., 1996; Packer et al., 1997; Plioplys and Plioplys, 1997; Rigden et al., 1998; Singh et al., 2002).

The rebuilding of cytoplasmic and mitochondrial membranes through supplementing with ω-3 fatty acids could also be included in a nutritional strategy (Behan et al., 1990; Nicholson, 2003). Essential fatty acids (EFAs), particularly the long-chain omega 3 fatty acids (EPA & DHA), are key for healthy mitochondrial membranes and activity and offer the potential of lowered inflammatory potential. Ogawa *et al* (1992) found low levels of polyunsaturated fatty acids (PUFAs) in CFS patients with immunological abnormalities. Some patients have shown favorably responses to EFA supplementation (Behan et al., 1990; Nicholson, 2003). However, timing the introduction of EFAs may be important. Nicholson (2003) points out that if PUFAs are given to patients with substantial processes of oxidative stress before the oxidative stress is reduced, a "biological rancidity" can occur through the peroxidation of the PUFAs.

Magnesium has also improved CFS symptoms in some patients (Abraham et al., 1992; Cox et al., 1991; Russell et al., 1995). Erythrocytic magnesium (Mg⁺⁺) has been found to be low in CFS patients. Supplementation with Mg⁺⁺ improved energy function, cognition, and sleep while it decreased fatigue. However, at least in one study, these results were not sustained over time (Cox et al., 1991).

As previously mentioned, the HPA axis commonly demonstrates downregulation in CFS patients (Komaroff and Buchwald, 1998; Racciatti et al., 2001)

as well as low serum levels of dihydroepiandrosterone sulfate (DHEAS) (Cleare, 2003; McCoy, 1993). In attempts to treat the HPA axis deficiency that is so prolific in CFS, DHEA as a hormone precursor has been used. DHEA, when given in low doses, has shown improvements in patient's symptoms (McCoy, 1993).

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