Chronic fatigue syndrome: a review from the biomechanical perspective

Raymond N Perrin DO, MRO

Abstract

Recent advances in research into chronic fatigue syndrome (virological, psychological, immunological, epidemiological and neurophysiological) were reviewed. Other recent surveys on this disease have found faults with the methodology and findings of many research projects undertaken in the past few years. This study is from a biomechanical approach, based on clinical findings in an osteopathic practice and utilising established osteopathic concepts .

The paper does not go as far as prove the correlation between mechanical dysfunction and the onset of chronic fatigue syndrome. Rather, it attempts to demonstrate the interaction between the somatic and sympathetic components of this distressing disorder. Research studies, from around the world, that contain contradictory conclusions are explained logically using this mechanical perspective. These conflicting results are shown to be quite compatible, when viewed from a different angle.

The findings suggest the importance of considering any disruptive mechanical processes, especially within the thoracic spine, which may be playing a major aetiological role in the formation of chronic fatigue syndrome. Further clinical research, utilising basic methodological principles is desperately needed to substantiate the biomechanical hypothesis.

Key words: Chronic Fatigue Syndrome (CFS); Sympathetic Nervous system; Thoracic Spine:

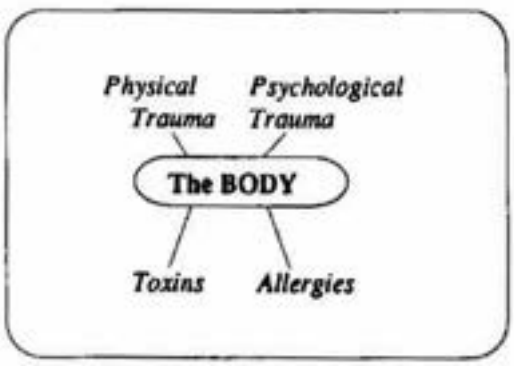
The therapies used at present to treat CFS are based on differing theories as to the cause of the disorder. Whatever the rationale behind their own particular theory, the one common denominator in all the treatments on offer is the removal or control of a stress producing factor. This element is damaging the body in some way or another, whether it be too much yeast[1], magnesium deficiency[2], or a simple viral infection[3]. A recent study at the National Institutes of Health in the USA concluded that there were many different aetiological agents, and that one sole virus was not to blame[4].

It is a well known fact that the build up of stress in a body eventually reaches a point that the slightest overload can cause a complete collapse of the organism. As Selye explained, a stressor produces an alarm reaction which produces a stage of resistance within the body, and finally a stage of exhaustion. This leads to the General Adaptation Syndrome, that occurs whatever the aetiological factors[5]. It is now more commonly called Stress syndrome.

Correspondence and reprint requests to:
Raymond N Perrin DO, MRO
83 Whittaker Lane
Prestwich
Manchester M25 5ET

The accumulation of any stress in the body can be due to many causative components (*diagram 1*), but by treating each individual stress factor separately the pressure on the body will be reduced but not totally alleviated. One has to combat all the causative factors together and reverse the whole process. It isn't easy. In fact it is so difficult to turn round the whole system that many practitioners admit defeat from the start, with many working on just one of the causes with limited success.

Fig 1: The build up of stress in the body



Some research papers on CFS have touched upon the neurological effects of the disease, and how the immune system is affected. In Spain, April '92, Castilla and colleagues noted a characteristic action of T-lymphocytes in CFS[6]. In June '92 a leading article in the Journal of The Louisiana State Medical Society states that evidence of immunological abnormalities existing in CFS indicates the presence of immune activation in CFS patients[7]. In August 1992, at the Minneapolis Medical Research Foundation, Minnesota, a relationship was established between immune stimulation and fatigue in mice[8]. This is elaborated later on in this paper. However the treatment recommended by many CFS specialists is to improve the hormonal and chemical balance via dietary means, and if necessary psychiatry or psychotherapy is offered to the patient. This is not to denounce these treatments as useless. They do help in numerous cases, but these experts are missing the point.

The neurological system that controls the hormonal and chemical balance of the body is the Autonomic Nervous System. If this system is working correctly, then it would be able to cope with extra stresses and strains after the body is detoxified or desensitised. Only then would psychotherapy help, and a healthy hypo-allergenic diet would bring about a permanent improvement in patients with CFS.

The sad fact is that in far too many cases there is little or no recovery after people subject themselves to the many varied dietary or chemical approaches of treatment. This is why I have had to treat many patients who have travelled far and wide for a cure.

The key is to find a total lasting remedy that helps the body cope with extra stress, and not just temporarily reduce the symptoms. If one looks at any stress factor as the "Infection", then the obvious course of action is to increase the body's defence in staving off this "infection". The immune system is neurologically controlled principally by the Sympathetic nerves.

A recent study in June '92 in Prince Henry Hospital, Little Bay, NSW, Australia, examined the relationships between the immunological and psychological dysfunctions of patients with CFS. This was demonstrated using a double blind trial of high dose intravenous immunoglobulin. Only those patients who received active immunotherapy showed a consistent pattern of correlations between improvement in depressive symptoms and markers of cell-mediated immunity.

The findings of this study supported the theory that the depressive symptoms in CFS occurred secondary to, or share a common pathophysiology with, an immunological disorder, and that depression was unlikely to be the primary dysfunction[9].

Exercise often helps fatigue associated with an overall lack of fitness or with depression, but exercise usually exacerbates fatigue in patients with CFS. In fact too much physical activity can trigger off a relapse in someone who is on the road to recovery. Patients are usually unhappy and frustrated, especially if the disorder drags on for months or years, with the patient being sent from pillar to post in search of a cure. This is very different from clinical depression.

Effective treatment of Fibrositis involves the use of antidepressants together with anti-inflammatory drugs. This treatment has been clinically shown to help the muscular pain in that condition[10]. The tenderness in fibrositis resembles the pain in some CFS cases and so similar treatment has been advocated[11].

The antiviral drug Acyclovir has been one drug to have had rigorous tests to see its efficacy in treating CFS. Many still accept and rely on the theory of a viral cause of the disease. Acyclovir has been successful against the Epstein-Barr virus, but double blind trials have shown it to have no greater effect on CFS than a placebo[12]. Evidence has shown that persistent viral infection occurs only in a small percentage of CFS cases[13].

Most patients on the Acyclovir drug trials reported that the improvement was short-lived and their symptoms returned soon after the treatment was completed.

In Japan the results of a recent study into the role of Epstein-Barr virus and CFS, concluded that there is a relationship between EBV and the syndrome, although the study did not demonstrate EBV as the sole aetiological agent[14]. This result differed from a more thorough virological study in the West.

After a three year research programme in the South West region of the USA, the conclusion reached was that CFS was not caused by any one single viral infection. Human T-lymphotrophic viruses I and II, Epstein-Barr virus, and human herpesvirus-6 were all excluded from a possible viral aetiological link with the monitored outbreaks of CFS[14].

In March '92 an Australian review on CFS stated that the evidence of chronic infection leading to the disease is unconvincing. The article continues that treatment should be based on supportive counselling coupled with psychiatric treatment, and that the patient should be encouraged to gradually increase everyday activity[15].

Reports of uncontrolled drug trials are now commonplace, and unlikely to help the medical profession's battle against CFS. This lack of proof as to the cause of the disorder, and the absence of the ultimate curative drug has led to other alternative treatment approaches. In Britain one of the most popular hypotheses is Chronic Candidiasis. The treatment is usually by oral antifungal Nystatin and Ketoconazole, plus

tic and pathological tests can all other possibilities be eliminated from the investigation.

In 1947 Irwin M Korr, J S Denslow and A D Krems measured the response to physical pressure applied to different segments in the spine. They showed that if external stress is continually applied to a particular area of the spine, a hypersensitive facilitated spinal segment is ultimately produced[21]. Further study led the researchers to suggest that in a facilitated segment, the autonomic nerves may also be affected. Later experiments showed that the surface vascularisation in the trunk is not uniform, and that local deviation in this cutaneous vasomotor activity appeared to be related to local changes in sympathetic nerve activity at corresponding segments of the spine[22].

In 1962 Dr Korr, H M Wright and P E Thomas demonstrated that postural changes in the spine produced alterations in the production of perspiration[23]. Korr et al., developed their hypothesis relating to sympathetic nerve involvement in disease processes. The first conclusions that they reached were as follows[24].

a) The manifestations of altered sympathetic activity represent an actual defect in the normal existing patterns of sympathetic activity.

b) These distortions are due to effects by impulses originating from either the viscera, or somatic sources.

c) Other components, such as adaptive or pathological changes in the body tissues of origin, and altered excitability within the central nervous system, may eventually become involved. This may directly affect local tissue without the expected route of the nerve impulses.

Further studies revealed that the areas of altered sympathetic activity appeared in apparently normal subjects. Korr suggested that this was due to subclinical bombardment of nerve impulses into the spinal cord. These impulses caused no symptoms themselves but, added to other stimuli affecting the same spinal segment, they could combine to cause problems[25].

Long lasting hyperactivity of innervating sympathetic pathways seems to be a prevailing theme in many clinical conditions, involving various organs and tissues[26].

Experiments in the former Soviet Union in 1957 and '58 demonstrated behavioural changes in rabbits after the normal functioning of the sympathetic nervous system was impaired. In 1961, following a sympathectomy, certain reflexes controlled by the central nervous system were shown to be diminished[27]. These two sets of experiments showed that there was definitely a connection between sympathetic nerves and the higher centres of the central nervous system. In other words, impaired sympathetic activity could lead to changes in the function of the brain in the patient, causing psychological symptoms developing with the advancing CFS.

At the Harbor UCLA Medical Centre in California, a SPECT scan revealed changes in the normal cerebral circulation in patients with CFS[28]. Although the changes in blood flow continue to baffle the research teams, this finding at the UCLA offers some visible proof to my hypothesis that part of the problem lies in the circulatory disturbances caused by the dysfunction of the sympathetic nervous system.

The only region's blood supply without specific sympathetic influence is the external genitalia. The arteries in this area fall under the control of the parasympathetic nervous system. Thus it will be no surprise to learn that the mechanics of sexual activity are not directly affected by CFS. Hormonal function affected by sympathetic disturbance can cause sexual problems. However, most sexual difficulties arise in CFS sufferers from a lack of desire, and a general loss of interest.

In the past many terms have been given to CFS type disorders, which are probably different names for the same disease. As early as 1871 in the American Journal of Medical Science, Dr J M DaCosta wrote a paper on a fatigue disorder that affected about three hundred soldiers during the American Civil War. The soldiers all had been in active service for quite a while. The symptoms listed were as follows:

1. Abdominal problems including diarrhoea and frequent indigestion
2. Palpitations usually induced by exertion
3. Chest pain
4. Shortness of breath, again aggravated by exertion
5. Rapid pulse
6. Headaches and dizziness
7. Disturbed sleep and
8. Excessive perspiration.

DaCosta also noted that when the soldiers' symptoms had eased and after they had returned to duty, their performance on the battlefield was of a low standard, and that they were unable to keep up with their healthy comrades. Dr DaCosta suggested that the cause of the problem was due to physical over-exertion and stress of the body, leading to an irritation of the heart. He proposed that the condition was sustained due to an imbalance in the nerve supply to the heart[29].

The innervation of the heart DaCosta referred to is predominantly via the sympathetic nerves from the upper thoracic region which synapse in the cervical sympathetic ganglia. (The parasympathetic vagus also aids the heart beat.) DaCosta's syndrome was also known as "Irritable Heart", and was also recognised in the Crimean War. Sir Thomas

Lewis, in 1920, wrote a paper noting similar cases during the First World War which he labelled "Effort Syndrome". Lewis concluded that an infection was at the root of the problem[30]. It was also known by the term Neurocirculatory Asthenia[31].

However, physical over-taxing of the body is being viewed as a common aetiological factor in CFS. In a recent study in the UCLA's School of Medicine, Puffer and McShane concluded that an athlete's motivation to succeed may lead to over-training which can eventually manifest itself as CFS[32].

The performance of the sympathetic system can be greatly affected by mechanical and postural strain to the mid section of the spine, from the 1st thoracic vertebra to the 2nd lumbar segment.

The concept of the primary machinery of the body being the muscular-skeletal system, with the internal organs being secondary and supportive, is a fundamental principle of osteopathic philosophy[33]. The role of the sympathetic nervous system is to co-ordinate this function of the viscera, via impulses from the muscular skeletal system, thus allowing the healthy existence of the whole body.

Rapid adjustments in accordance with levels of exertion and posture are orchestrated largely by the sympathetic nerves. The parasympathetic system makes long term adjustments maintaining and replenishing stores of nutrients and fuel which have been utilised under the direction of the sympathetic system. In other words both sections of the autonomic nervous system work in conjunction with each other. From this viewpoint, illness results from the inconsistency between demands of the neuromuscular-skeletal system (the Primary Machinery) and the ability to maintain adequate provision for the normal functioning of all the bodily systems. Thus a patient requires rest when ill, reducing demand until this disparity is corrected.

Traditional medicine places more emphasis on demands from the internal organs. However, by virtue of their mass and their rapidly changing metabolic rate, the muscles are the main consumers of the body.

Anatomically there is an intimate relationship with part of the somatic and sympathetic nerves. The motor neurons contain fibres that lie alongside the preganglionic fibres of the sympathetic nerves as they leave the spinal cord. The postganglionic sympathetic fibres also connect with the motor nerves as they travel down to the target tissues. Sympathetic nerves are also equally sensitive to stimuli from either sensory inputs, higher centres or interspinal nerves. Also, since spinal nerve roots contain both somatic and sympathetic fibres, both are vulnerable to any mechanical trauma.

The sympathetic sensory nerves are excited by painful states in the internal organs. The reduction of blood flow when there is spasm in the organ, leads to a chemical irritation stimulating the preganglionic sympathetic nerves in the spinal cord. This leads to physiological changes within the target organs e.g. dilation of blood vessels resulting in increased circulation. The neighbouring motorneurones are also excited prompting a sustained muscular contraction.

If the sympathetics are over-stimulated the following effects occur[34].

1. On muscles: The force of muscle contraction is increased and there also appears to be a delay in the onset of fatigue in over-stimulated muscles.
2. There is an increase in excitability of sensory mechanisms.
3. The bone marrow which is highly rich in sympathetic supply is stimulated to fight any disease.
4. The endocrine system which is under the influence of the sympathetic nerves is stimulated to release many hormones.

It therefore follows that if there is an impairment in sympathetic control the opposite effects may occur, thus reducing muscle contraction, increasing fatigue, reducing sensation and lowering the resistance to disease. Sympathetic stimulation only modifies the inherent physiology rather than introducing new qualities, so that each tissue responds in its own particular way.

This is why CFS can affect different patients in various ways. Some sympathetic paths may be functioning correctly, others may be overactive, whilst in other cases they may be severely blocked. The common factor is that with any form of Chronic fatigue syndrome there is a general dysfunction of the sympathetic nervous system as a whole, causing widespread symptoms of ill-health within the body. Some of the symptoms are due to an over-activity of the sympathetic nerves , other effects relate to a reduction of sympathetic activity. A better term for CFS would therefore be "Chronic Sympathetic Dysfunction Syndrome".

This writer's hypothesis does not rule out the possibility of viruses being involved in the pathology of CFS. It could be said that the sympathetic nervous system's dysfunction leads to a reduction in the body's immune system. This in turn results in the body as a whole being susceptible to viral infections of more than one type. This is why research into a viral cause has been going on for some years, with many different viruses being suspected of playing a role in the establishment of the disease[35].

The main influence on the sympathetic nervous system is

thought to emanate from the lateral and posterior nuclei of the hypothalamus[36]. Experiments have shown that decerebrated animals still possess cardiovascular reflexes. This demonstrates that the hypothalamus is not essential for sympathetic activity, but it probably plays a role in long term metabolic regulation[37]. There are also impulses from the frontal lobes, independent of the hypothalamus. Injury to the cortex has sometimes produced vasomotor effects in the victim.

The homeostatic function of the sympathetic nervous system is clearly demonstrated when there is a break of the spinal cord above the 1st thoracic vertebra following a major trauma. The lesion of the cord at this level would cut off the whole thoraco-lumbar sympathetic outflow from higher control. After the accident, tilting the patient from supine to an upright position would lead to:-

1. Decrease in blood pressure.
2. Increase in the rate of the pulse.
3. Loss of consciousness.

These effects occur since there is no compensatory control of the blood vessels to adjust to the change of the position. The skin blood vessels also do not adapt to any change of body temperature, i.e. there is no vasodilation or sweating. Also, if cold there is no shivering of the muscles controlled by nerves below the spinal lesion. It is important to note that the lower the level of the damage to the cord the smaller the disturbance of the autonomic control[38]. The results of a ganglionectomy include widespread and lasting dilation of the arterial supply in the limbs, especially in the skin[39].

Obviously, if the symptoms of chronic fatigue syndrome are due to a dysfunction of the sympathetic nervous system, a sympathectomy is not the desired treatment, as although the peripheral circulation may improve, the other effects of cutting off the sympathetic control would be detrimental.

If the sympathetic disturbance lay at the root of CFS, then it would be only correct to assume that drugs that act on the sympathetic nerve transmissions would affect the symptom picture of CFS sufferers. The action of MAOIs is to inhibit some of the autonomic neurotransmitters. The metabolism of adrenaline is also inhibited by these drugs. Not surprisingly, MAOIs have been shown to help improve the symptoms of CFS[41].

Furthermore, E Slater and M Roth have recorded that some patients suffering from CFS have felt normal on a dose of dexamphetamine[41]. The good performance of the dexamphetamine in the treatment of CFS demonstrates that depression is not the sole cause of the illness. Peripherally, amphetamines produce their stimulant action by displacing noradrenaline at the terminals of the sympathetic nerves. In the central nervous system the transmitter substance dopamine is also released due to the activity of amphetamine. The main action of amphetamine is the presynaptic release of noradrenaline and dopamine in the brain which leads to increased alertness and euphoria. A stimulant action on the descending adrenergic pathways leads to an increase of muscular energy. Thus one can easily see why amphetamines have such a beneficial affect on patients with CFS. Unfortunately, they possess many damaging side effects.

The main factor concerning the aforementioned drugs is that antidepressants and nervous stimulants both seem to have a beneficial effect on CFS. This clearly shows that there are parts of the nervous system that are in disarray. The problem, in my opinion, is with the ability of transmitting nervous impulses along the autonomic fibres, specifically the sympathetic nerves. The precise region of this disturbance may be at the higher centres within the hypothalamus or cortex. It may be within the endocrine centres of the pituitary or adrenal glands, or it may be in the spinal cord, at the ganglia or in the postganglionic fibres of the sympathetic nervous system.

My own clinical findings have led me to conclude that the major area of dysfunction lies at the thoracic and upper lumbar spine affecting the ganglionated sympathetic trunks, and the nerves around these ganglia.

Preganglionic sympathetic nerve fibres emerge from the spinal cord via the ventral roots of the corresponding spinal nerves, along the rami communicantes to the ganglia on the sympathetic trunks. Postganglionic non-myelinated fibres, pass from the sympathetic trunk via the grey ramus communicans to corresponding spinal nerves lying just proximal to the white ramus communicans. These fibres then enter the ventral and dorsal rami of the spinal nerves[42].

One can see that anatomically the somatic and sympathetic systems are integrally connected at the spine. It therefore follows that any mechanical damage to the thoracic and upper lumbar vertebrae may result in a detrimental effect on the sympathetic nerves. This dysfunction will influence either part or all of the sympathetic nervous system, depending on the source of the mechanical injury.

A detailed examination of the spinal movements and the overall posture of patients with Chronic Fatigue Syndrome will reveal, to the trained practitioner, long-standing problems in the spine, specifically in the thoracic and upper lumbar regions.

Unfortunately, there has been no prior data correlated to demonstrate the connection between the spinal mechanics and the incidence of CFS. With only anecdotal evidence and clinical findings to go on, I decided to review the cases that I had seen over the last few years, where the patients had either presented with CFS type symptoms, or had been

already diagnosed as suffering from the disorder. Below is a table showing the relevant details of forty such patients, 20 female and 20 male. The files were randomly selected from patients seen in the past three years. The first column demonstrates that CFS can strike people of all ages. Column 2 shows the variety of different occupations of the patients. The majority of these vocations place extra strain on the thoracic spine, with the person constantly exerting repetitive strain on the upper part of the body.

Fig 2a. Female Patients

Age	Occupn	Area of Dysfunction In Thoracic Spine	Acute Onset of Back Sympt-oms	Chron. Irritatn of Thora-cic Spine	Yrs between Onset of Back Problems & CFS Symptoms
35	Nurse	ALL Ts	4yrs	4yrs	3
74	H'wife	ALL Ts	***	35yrs	28
17	Student	Upper+Lower	14mths	14mths	3mths
49	Clerk	ALL Ts	30yrs	30yrs	4
21	Student	Upper Ts	***	6yrs	5.5
20	T-sales	Upper Ts	***	10yrs	9.5
31	VDU's	Lower Ts	***	13yrs	4
51	H'wife	Upper+Mid	***	13yrs	9
40	Bk-kpr	Upper Ts	***	4.2yrs	4
40	Teachr	ALL Ts	***	14yrs	7
60	Clerk	ALL Ts	15yrs	15yrs	7
29	SocWk	Upper Ts	***	4.5yrs	4
45	Teachr	ALL Ts	21yrs	21yrs	20
32	Shpkpr	ALL Ts	***	7yrs	2
48	H'wife	Upper Ts	***	7yrs	3
48	Teachr	Upper Ts	***	10yrs	4
52	Ex-Tea	Upper Ts	***	10yrs	5
28	Sec	Upper Ts	***	10yrs	6
22	H'wife	Upper+Mid.	15yrs	15yrs	11
35	H'wife	Mid Ts	***	10yrs	9.5

Fig 2b. Male Patients

Age	Occupn	Area of Dysfunction In Thoracic Spine	Acute Onset of Back Sympt-oms	Chron. Irritatn of Thora-cic Spine	Yrs between Onset of Back Problems & CFS Symptoms
46	Teacher	ALL Ts	6yrs	6yrs	0
46	Optic'n	ALL Ts	***	10yrs	8
38	Dentist	Upper Ts	9yrs	9yrs	8.8yrs
25	Student	Upper Ts	***	2yrs	1.5
30	Desgnr	Upper+Mid	8yrs	8yrs	4
36	Shpkpr	Upper+Mid	9yrs	9yrs	5
16	Student	Upper Ts	***	4yrs	3
35	Shpkpr	Upper Ts	***	5yrs	4
27	Fotbllr	Upper Ts	***	5yrs	1
31	Ex-Cyc	ALL Ts	***	8yrs	1
42	Teachr	ALL Ts	20yrs	20yrs	17
35	Studnt	ALL Ts	***	12.3yrs	4mnths
20	Studnt	Lower Ts	***	3yrs	1.5
45	Joiner	Upper Ts	5yrs	5yrs	3
31	Mangr	Upper+Mid	***	16yrs	11
26	Bnk-cl	Upper+Mid	***	12yrs	1mnth
29	Sc'ntis	Upper Ts	7yrs	7yrs	1
60	Film-Dir	Upper Ts	***	20yrs	19.5
40	Teacher	Upper Ts	***	1.5yrs	1
49	Chapln	Total Ts	***	8yrs	5

All of the patients had a particular dysfunction in the dorsal region, whether it was inflammation, kyphosis or just a restricted area. Column 3 of the table shows if all or part of the thoracic spine was affected.

The data above reveals which patients suffered from a previous acute injury that precipitated any back problem. If the onset of the spinal problem followed an acute injury, then the time the injury occurred is recorded in column 4. i.e. the number of years ago that the accident happened. If the onset of the back pain was gradual and insidious, due to constant repetitive trauma, or the aetiology was postural, then three *s have been placed in this column. Column 5 lists the total time that the patient has been suffering with the spinal symptoms, whether it be stiffness, pain or severe spondylitis.

The final column is the most significant, as it demonstrates how the length of the interval between the onset of the back problems and the commencement of CFS symptoms is related to the nature of the aetiology.

A review of the data compiled above leads to the following conclusions:

a) The occupations seemingly affected most by CFS, in the patients studied, are Teachers (7 patients), Secretarial /clerical (6 patients), and students (6 patients). These occupations, in particular, place a major postural strain on the upper spine. Of the total 40 patients reviewed, 27 [i.e. 67.5%] were involved in jobs that put extra demand on the thoracic spine, more than any other region of the back.

b) The average time-lag between the onset of back pain and the onset of CFS seems to differ slightly, depending on the original cause. If at first there was an acute injury, the average time-lag is 6.47 years. If however the aetiology is postural, or due to a chronic repetitive strain, then the average time-lag is 5.83 yrs. When the sympathetic nervous system is under constant bombardment from repetitive afferent impulses, then a dysfunction of the system is more likely to occur compared to one individual trauma, unless the acute trauma was a particularly severe injury. This will explain the shorter time-lag in most of the patients with chronic back pain.

Obviously, more clinical and patho-physiological research is required to verify and ratify the above hypothesis. However, it is my belief that with further studies, the outcome within the scientific world will prove a definite connection between the mechanical dysfunction of the thoracic spine and the process leading to the sympathetic disarray we know as Chronic Fatigue Syndrome.

References

1. Anderson JA, Chai H. Claman HV. Candiasis Hypersensitivity Syndrome. Journal of Allergy & Clinical Immunology 1986; 78:271-273. Zimmerman MH, Webber E. Candida. a 20th Century Disease. Canadinn Medical Association Journal 1986; 133: 985-966. Renfro L, Feder HM, Lane TJ, Manu P, Matthews DA. Yeast Connection Among 100 patients with Chronic Fatigue Syndrome. American Journal of Medicine 1989; 86: 165-168. Dawes B. & Downing D. Why ME; London: Grafton, 1989.
2. Clage JE, Edwards RH, Jackson MJ. Intravenous Magnesium Loading in Chronic Fatigue Syndrome (a letter). Lancet, July 1992; 340 (8811): 124-125.
3. Berneman ZN, Gallo RC, Ablasi DV, Frenkel N, Katsafanas G, Kramarsky B, Brus I. Human Herpes-virus 7. Journal of Infectious Disease (U.S.) Sep 1992; 166 (3): 690-691.
4. Levine PH, Jacobson S, Pocinki AG, Cheney P, Peterson D,Connelly RR, et al Clinical, Epidemiological, And Virological Studies In Four Clusters Of Chronic Fatigue Syndrome. Arch. Intern. Med.(U.S.) Aug 1992; 152(8): 1611-1616.
5. Selye H. General Adaptation Syndrome. Nature, July 4, 1936. Selye H. The Stress Of Life. New York: McGraw-Hill.
6. Castilla A, Subira ML, Civeira MP, Cuende JI. Surface T- Lymphocyte Markers And Monocyte Dysfunction In The Chronic Fatigue Syndrome. An. of Intern. Med. (Spain) Apr 1992; 9(4): 207-8.
7. Winters EG, Quinet RJ. Chronic Fatigue Syndrome. Journal of Lousiana State Medical Society (U.S.) Jun 1992; 144 (6): 260-270.
8. Chao C, DeLaHunt M, Hu S, Close K, Peterson PK. Immunologically Mediated Fatigue: A Murine Model. Clin Immunol Immunopathol (U.S.) Aug 1992; 64 (2): 161-165.
9. Hickie I, Lloyd A, Wakefield D. Immunological and Psychological dysfunction in patients receiving Immunotherapy for Chronic Fatigue Syndrome. Australia & New Zealand Journal of Psychiatry (Australia) June 1992; 26 (2): 249-256.
10. Bennett RM, Gatter RA, Campbell SM, Andrews RP, Clark SR et al. A Comparison of Cyclobenzaprine & Placebo in The Management of Fibrositis: A Double-blind Controlled Trial. Goldenberg DL, Felson DT, Dinerman H. A Randomized Controlled trial of Amytriptyline & Naproxen in The Treatment of Patients With Fibromyalgia. Arthritis & Rheumatism 1986; 29: 1371-1377.
11. Jones JF, Straus SE. Chronic Epstein-Barr Virus Infection. Annual Review of Medicine 1987; 38: 195-209.
12. Gantz NM, Holmes GP. Treatment of Patients With Chronic Fatigue Syndrome. Drugs 1989; 38 (6): 855-862
13. Straus SE, Dale JK, Ablashi DV, Salahuddin ZS, Gallo RC, et al. The Inoue-Melnick Virus, Human Herpesvirus Type 6, And the Chronic Fatigue Syndrome. Annals of Internal Medicine 1989; 110: 92-93. Behan PO, Behan WMH, Bell EJ. The Post-viral Fatigue Syndrome: An Analysis of The Findings in 50 Cases. Journal of Infection; 10: 211-222.
14. Kawai K, Kawai A. Studies On The Relationship Between Chronic Fatigue Syndrome And Epstein-Barr Virus In Japan. Intern. Med. (Japan) Mar 1992; 31(3): 313-318.
15. Holmwood C, Shannon C. Chronic Fatigue Syndrome: A Review From The General Practice Perspective. Australian Family Practitioner 1992; 21 (3): 278-9 & 283-5.
16. Quinn JP, Venezio FR. Ketoconazole And the Yeast Connection. Journal of the American Medical Association 1986; 255: 3250.
17. Cox IM, Campbell MJ, Doeson. Red Blood Cell Magnesium And Chronic Fatigue Syndrome. Lancet 1991; 337: 757-760.
18. Durlach J. Chronic Fatigue Syndrome And Chronic Primary Magnesium Deficiency. Mag. Res.(England). Mar 1992; 5 (1): 68.
19. Cunningham DJC. The Control System Regulating Breathing In Man. Quarterly Reviews of Biophysics 1973; 6: 433-484. Torrance RW, ed. The Arterial Chemoreceptors. Oxford: Pergamon, 1968. Johnson RH, Spalding JMK. Disorders of The Autonomic Nervous System. Oxford: Blackwell, 1974. Whelan RF. Control of The Peripheral Circulation In Man. Springfield, Illinois: Charles C. Thomas, 1967.
20. Bell GH, Emslie-Smith D, Paterson CR. Textbook Of Physiology. 10th Edition, Edinburgh: Churchill Livingstone, 1980, p.343. Merton PA, Marsden CD, Morton HB. Is The Human Stretch Reflex Cortical Rather Than Spinal? Lancet 1973; 1: 759-761.
21. Korr IM, Denslow JS, Krems AD. Quantitative Studies Of Chronic Facilitation in Human Motoneuron Pools. American Journal Of Physiology 1947; 150: 229-238.
22. Korr IM, Wright HM, Thomas PE. Local & Regional Variations in Cutaneous Vasomotor Tone Of The Human Trunk. Journal Of Neural Transmission 1960; 22 (3): 34-52.
23. Korr IM, Wright HM, Thomas PE. Effects Of Experimental & Myofascial Insults On Cutaneous Patterns Of
24. Sympathetic Activity In Man. Journal Of Neural Transmission 1962; 23 (22): 330-355.
25. Korr HM, Wright HM, Chase JA. Cutaneous Patterns Of Sympathetic Activity in Clinical Abnormalities Of the Musculoskeletal System. Journal of Neural Transmis-

sion 1964; 25: 589-606.
26. Korr IM, ed. Sustained Sympatheticonia As A Factor In Disease: The Neurobiological Mechanism In Manipulative Therapy; New York: Plenum 1978, 229-268.
27. Koramian AI. Influence Of The Sympathetico-adrenal System Upon Reflex Activity At Higher Levels Of The C.N.S.Sechenov Physiol. J. (Russian Trans.) 1958; 44: 285-295. Sollertinskaya TN. The Effect On The Electrical Activity Of The Cerebral Cortex After Removal Of The Superior Sympathetic Ganglia. Dorklady Biol. Sci.(Transl.) 1957; 112: 145-147.
28. Cowly G, Hager M, Joseph N. Chronic Fatigue Syndrome, A Modern Medical Mystery. Newsweek Nov. 1990; CXVI (20): 34-40.
29. DaCosta JM. A Clinical Study of A Form Of Functional Cardiac Disorder And Its Consequences. American Journal Of Medical Science 1871; 61: 17-52.
30. Lewis T. The Soldiers Heart And The Effort Syndrome. New York: Paul B. Hober, 1920.
31. Oppenheimer, Levine. Report On Neurocirculatory Asthenia And Its Management. Military Surgeon 1918; 42: 409-426;711-719.
32. Puffer JC, McShane JM. Depression And Chronic Fatigue In Athletes. Clin. Sports Med. (U.S.) Apr 1992; 11 (2): 327-328.
33. Korr IM. The Sympathetic Nervous System As Mediator Between The Somatic And Supportive Process. The Physiological Basis Of Osteopathic Medicine 1970; 21-38.
34. Korr IM. The Spinal Cord As Organizer Of Disease Processes: The Peripheral Autonomic Nervous System. Journal Of American Osteopathic Association Oct 1979; 79: 82-90.
35. David AS, Wessely S, Pelosi AJ. Postviral Fatigue Syndrome, Time For A New Approach. British Medical Journal March 1988; 296: 696-698.
36. Burn JH. The Autonomic Nervous System, 4th Edn. Oxford: Blackwell. 1971
37. Reichler S., Baldessarini RJ, Martic JB. The Hypothalamus. New York: Raven 1978.
38. Guyton. Textbook Of Medical Physiology , 8th Edn. London: W.B. Saunders 1991.
39. Bell GH, Emslie-Smith D, Paterson CR. Textbook Of Physiology, 10th edn. Edinburgh: Churchill Livingstone, 1980.
40. Gantz NM, Holmes GP. Treatment Of Patients With Chronic Fatigue Syndrome. Drugs 1989; 38(6): 855-862.
41. Slater E. Roth M. Mayer-Gross Clinical Psychiatry, 3rd Edn. London: Bailliere 1977.
42. Warwick R, Williams PL, Eds. Gray's Anatomy. 35th edn. Edinburgh: Longman 1973.