# THE INVOLVEMENT OF CEREBROSPINAL FLUID AND LYMPHATIC DRAINAGE IN CHRONIC FATIGUE SYNDROME (CFS/ME)

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"Sometimes our light goes out but is blown into flame by another human being. Each of us owes deepest thanks to those who have rekindled this light"

Albert Schweitzer (1875-1965)

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In memory

of

Ian McAnulty

(1948 - 2000)

# DECLARATION

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# ABBREVIATIONS

| | |
|---|---|
| ACTH | Adrenocorticotrophic hormone |
| AfME | Action for myalgic encephalomyelitis |
| ANS | Autonomic nervous system |
| AOA | American osteopathic association |
| AP | Anterior-posterior |
| ARA | Arachidonic Acid |
| ATP | Adenosine triphosphate |
| BAI | Beck's anxiety inventory |
| BDI | Beck's depression inventory |
| BIT | Bojungikki-tang |
| BPM | Beats per minute |
| CAB | Carotid basilar |
| CBT | Cognitive behavioural therapy |
| CCFP | Chronic ciguatera fish poisoning |
| CCHS | Chronic candidiasis hypersensitivity syndrome |
| CDC | Centre for disease control and prevention |
| CFC | Chlorofluorocarbon |
| CFIDS | Chronic fatigue immune deficiency syndrome |
| CFS | Chronic fatigue syndrome |
| CHS | Clinical history schedule |
| CNS | Central nervous system |
| CP | Control patient |
| CRH | Corticotropin releasing hormone |
| CRI | Cranial rhythmic impulse |
| CSF | Cerebrospinal fluid |
| CT | Computerised tomography |
| CV4 | Compression of fourth ventricle |
| DF | Degrees of freedom |
| DHA | Docosahexonoic Acid |
| DHEA | Dehydroepiandrosterone |
| DSM | Diagnostic and statistical manual of mental disorders |
| DWMH | Deep white matter hyperintensity |
| EBV | Epstein Barr virus |

| | |
|---|---|
| EFA | Essential Fatty Acid |
| EMG | Electro myography |
| FES | Functional electrical stimulation |
| FFT | Fast Fourier transformation |
| FLAIR | Fluid attenuated inverse recovery |
| FH | Foot-head |
| FORME | Fund for osteopathic research into myalgic encephalomyelitis |
| FOV | Field of view |
| GWVs | Gulf War veterans |
| HADS | Hospital anxiety and depression scale |
| HC | Healthy control |
| HPA | Hypothalamic pituitary adrenal |
| HVLA | High velocity low amplitude |
| HVT | High velocity thrust |
| IBS | Irritable bowel syndrome |
| ICD | International statistical classification of diseases |
| ICP | Intracranial pressure |
| iEMG | Integrated electromyography |
| IGC | Item group checklist |
| IGF | Insulin-like growth factor |
| IL | Interleukin |
| LC | Locus coeruleus |
| MAP | Muscle action potential |
| ME | Myalgic encephalomyelitis/encephalomyelopathy |
| MIA | Membrane immunobead assay |
| MIP | Maximum intensity projection |
| MMR | Measles mumps rubella |
| MPTP | 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridinium |
| MR | Magnetic resonance |
| MRI | Magnetic resonance imaging |
| NADH | Nicotinamide adenine dinucleotide H |
| NC | Normal control |
| NIAC | Neuro imaging analysis centre |
| NK | Natural killer |
| NMDA | N-Methyl-D-Aspartate |

| | |
|---|---|
| OIS | Osteopathic information service |
| PC | Phased contrast |
| PCB | Polychlorinated biphenyl |
| PET | Positron emission tomography |
| PFRS | Profile of fatigue related states |
| PGi | Paragigantocellularis |
| PPU | Peripheral pulse unit |
| PSE | Present state examination |
| PVFS | Post-viral fatigue syndrome |
| PVH | Periventricular hyperintensity |
| PVN | Paraventricular nucleus |
| RL | Right-left |
| Rnase L | Ribinuclease L |
| ROI | Region of interest |
| RP | Research patient |
| RSD | Reflex sympathetic dystrophy |
| RV | Research volunteer |
| SCAN | Schedules for clinical assessment in neuropsychiatry |
| sEMG | Surface electromyography |
| SH-SY5Y | (Cell line for Human Neuroblastoma) |
| SNS | Sympathetic nervous system |
| SPECT | Single photon emission computerised tomography |
| SPET | Single positron emission tomography |
| SPIR | Spectral re-saturation with inversion recovery |
| Tc | cytotoxic T lymphocytes |
| TD | Thoracic duct |
| TE | Time to echo |
| Th | T-helper cells |
| TR | Time of repetition |
| WMH | White matter hyperintensities |
| YOA | Years of age |

# ABSTRACT

A novel osteopathic treatment has been discovered during the clinical practice of the author which alleviates many of the symptoms of chronic fatigue syndrome (CFS) known in the UK as CFS/ME. The efficacy of this manual approach was tested using two separate clinical trials. The first examined the change in the symptoms following a year of treatment. The second repeated the first study and examined the possible mechanisms of the improvement. The studies were designed to develop a greater understanding of the disorder, for which there is much scientific uncertainty regarding the cause, diagnosis and treatment.

Phase 1 of the research trials included self report questionnaires to examine overall symptom change. With post-exercise fatigue being a major symptom of CFS/ME, the treatment protocol was best evaluated by determining its effects on muscle function which was analysed utilising isometric testing of the knee extensor muscles measuring the impulse torque.

The second trial, which included the same self report questionnaires assessing symptom relief as in the initial trial, was divided into two parallel phases. Phase 2 primarily took the form of brain analysis using magnetic resonance imaging (MRI) to confirm if brain abnormalities seen in previous research were found in sufferers of CFS/ME. No cerebral abnormality was detected in the patient group. Central lymph scans were also carried out showing a possible trend of enlargement in CFS/ME sufferers. In the other part, phase 3, isometric tests were repeated with more accurate equipment than in phase 1. Integrated EMG and median frequency of the power spectrum were measured using surface electromyography (sEMG).

Overall this study has provided strong evidence that an important component of CFS/ME involves a disturbance of lymphatic drainage of the brain and muscles. The novel osteopathic treatment developed by the author has been statistically validated in both phases of the study, emphasising the need to focus future research on the biomechanical aspects of this disorder.

# Chapter 1

# 1 General Introduction

## 1.1 CFS/ME: A definition

Chronic fatigue syndrome (CFS) or Myalgic Encephalomyelitis (ME) as it has been known in the UK since the 1950s (Ramsay, 1978; Ramsay and O'Sullivan, 1956) is a clinically accepted condition now referred to in Britain as CFS/ME (Hutchinson *et al.*, 2002). It is characterized by generalised abnormal muscle fatigue that occurs after relatively mild activity. Other common symptoms include sleep disturbances, headaches, cognitive dysfunction, depression, increased sensitivity to light and sound, back and neck pain, sore throat, and irritable bowel and bladder pain (Ramsay, 1978; Acheson, 1959; Macintyre, 1992; Dowsett *et al.*, 1990).

The use of the name "chronic fatigue syndrome", compared with alternative terms, is not intended in any way to trivialize this illness. However without adequate scientific justification the use of the term M.E. (Myalgic Encephalomyelitis/ Myalgic Encephalomyelopathy) which is not widely used except in the UK and Canada, could lead to confusion and will substantially undermine the progress that has been made by the original research. The author supports changing the name when more is known about the underlying pathophysiological process or processes associated with this syndrome. The joint term CFS/ME has been agreed upon in the recent Chief Medical Officers report into the condition (Hutchinson *et al.*, 2002) and thus it was felt by the author to be the most suitable name at this present time.

CFS/ME, according to The CDC, is currently defined by the presence of the following: Clinically evaluated, unexplained persistent or relapsing chronic fatigue that is of new or definite onset (has not been lifelong); is not the result of ongoing exertion; is not substantially alleviated by rest; and results in substantial reduction in previous levels of occupational, educational, social, or personal activities.

In addition, the concurrent occurrence of four or more of the following symptoms, all of which must have persisted or recurred during 6 or more consecutive months of illness and must not have predated the fatigue.

Self-reported impairment in short-term memory or concentration severe enough to cause substantial reduction in previous levels of occupational, educational, social, or personal activities; sore throat; tender cervical or axillary lymph nodes; muscle pain; multijoint pain without joint swelling or redness; headaches of a new type, pattern, or severity; unrefreshing sleep; and malaise lasting more than 24 hours following exertion (Fukuda *et al.*, 1994).

Another frequently used set of diagnostic criteria used in this country is the UK (Oxford) criteria (Sharpe *et al.*, 1991) which is similar to the CDC definition mentioned above but differs in the number of symptoms needed to confirm the diagnosis and most significantly allows for minor psychiatric comorbidity to exist.

## 1.2 CFS/ME: A brief history

In the past, many terms have been given to CFS type disorders which are probably different names for the same disorder. As early as 1871 union army doctor J. M. DaCosta described a fatigue disorder that affected about three hundred soldiers during the American Civil War. The soldiers had all been in active service for quite a while.
The symptoms listed were as follows:
Abdominal problems, including diarrhoea and frequent indigestion.
Palpitations usually induced by exertion.
Chest pain.
Shortness of breath, again aggravated by exertion.
Rapid pulse.
Headaches and dizziness.
Disturbed sleep.
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 low standard and that they were unable to keep up with their healthy comrades. DaCosta suggested that the cause of the problem was due to physical over-exertion and physical 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 (DaCosta, 1871). The 'innervation of the heart' DaCosta referred to is predominantly part of the sympathetic nervous system, with the parasympathetic vagus innervation also controlling the heart beat. DaCosta's syndrome, also known as "Irritable Heart", was recognised in the Crimean War. Sir Thomas Lewis wrote a paper in 1920 noting similar cases during the first World War which he labelled "Effort Syndrome" also known as Neurocirculatory Asthenia (Oppenheimer and Levine, 1918). Lewis concluded that an infection was at the root of the problem (Lewis, 1920).

Since Lewis, a number of physicians, neurologists, cardiologists and others have searched for the cause, constantly redefining this mysterious disorder. Eminent psychiatrists have pointed to a possible psychological source of the disease. From the label "Yuppie Flu" of the 1980's to the totally dismissive attitudes of some practitioners, many patients feel isolated and depressed as a result of ignorance. The inability of the health-care profession as a whole to legitimise this illness has been shown to aggravate psychiatric morbidity in sufferers (Lehman *et al.*, 2002). Sufferers have been labelled as unmotivated and school or work-phobic although clinically one sees that most patients are well motivated, high achieving type 'A' personalities.

To add insult to injury research findings continue to lay the blame of CFS/ME on the patient's inability to cope with daily problems (Van Houdenhove *et al.*, 1995), fear of physical activity (Silver *et al.*, 2002), altered perception of the sufferer (Metzger and Denney, 2002) or worse, as a result of parental attitude such as maternal overprotection in childhood (Fisher and Chalder, 2003). It remains a condition that attracts controversy since many of the symptoms are non-specific, common to many other illnesses including psychiatric disorders. However atypical depression, which is a common feature of the disease, has been viewed as a sickness behaviour seen in many chronic illnesses rather than

an affective disorder (Van Hoof *et al.*, 2003). An Australian study on 23 matched CFS/ME patients demonstrated an insignificant effect on cognitive ability due to depression and showed similar anxiety scores in the healthy group and the sufferers (Short *et al.*, 2002). Nevertheless it still continues to be an enigma that confounds medical research to the extent that it has recently been conceptualised as "The Black Hole" of medicine (Eidelman, 2003). Apart from the strain of suffering from a severely debilitating illness, much emotional stress emerges from the refusal of others to accept the validity of the illness leading to many strained relationships at home, work and school and with members of the social services and medical profession (Shafran, 1991).

## 1.3 The cost of CFS/ME

The prevalence of CFS/ME in the UK has been estimated as 0.5% when comorbid psychological disorders were excluded (Wessely *et al.*, 1997) The government's working group in January 2002 estimated that a general practice with 10,000 patients is likely to have between thirty to forty CFS/ME sufferers (Hutchinson *et al.*, 2002). Prognosis of this complex disorder is recognised as highly variable. At 12 to 18 months, rates of improvement range from 11 to 64 % and worsening of symptoms range from 15- 20 %. However these rates are based on subjective self reported changes (Mulrow *et al.*, 2001). The economic impact on individuals in the form of informal care and lost employment is devastating (McCrone *et al.*, 2003). Statistical analysis recently carried out by the Survey and Statistical Research Centre at the Sheffield Hallam University revealed that CFS/ME annually costs the UK government around £3.5 billion in benefits payment, caring and loss of taxation (AfME, 2003). Thus on a global scale the impact of CFS/ME on society in both human and economic terms is of great magnitude.

## 1.4 Research into CFS/ME

Although many relatively small research projects have been carried out, financed mainly from private charitable trusts, pharmaceutical firms which are the main funders of medical research have tended to shy away from financing any major studies investigating CFS/ME. As demonstrated from present socio-economic research there is clearly no evidence to

justify this lack of interest compared with the research funding for other global diseases such as Aids (Pinching, 2003).

Some breakthroughs have been made which may soon mean clinical tests are available to objectively assess the severity of CFS/ME; such as the head-up tilt test using haemodynamic instability score (Naschitz *et al.*, 2003). Yet there are still no universally accepted investigative tests for this condition that have been validated in scientific studies. Thus from the diagnostic viewpoint there has been little movement in classifying the disease in over a decade (Holmes *et al.*, 1988). The problem of clinical diagnosis is compounded by the fact that the cardiopulmonary functional capacity of patients varies greatly (Vanness *et al.*, 2003).

The symptoms of CFS/ME typically become apparent following a common viral infection (Dowsett, 1990), or a less common infection such as the Q fever outbreak in the Midlands, UK in 1989 caused by *Coxiella burnetii*, although many other causative factors have been suggested. Vaccinations against cholera, tetanus, typhoid and influenza have been associated with the onset of CFS/ME (Lloyd *et al.*, 1988). Organophosphate pesticides have been suggested as an aetiological factor (Gershon and Shaw, 1961; Tahmaz *et al.*, 2003) as have other environmental toxins (Rogers, 1990; Dustan *et al.*, 1995). Patients with CFS/ME have been shown to have greater chemical sensitivity than healthy controls. They also have similar clinical presentations and are demographically analogous to those suffering from multiple chemical sensitivities (MCS) (Buchwald and Garrity, 1994; Fiedler *et al.*, 1996; Nawab *et al.*, 2000). It has also been observed that the psychological disturbances in CFS/ME occur secondary to, or share a common pathophysiology with immunological dysfunction ( Hickie *et al.*, 1992) However, in many cases there appears to be no apparent cause triggering the condition (Harvey, 1989). Diagnosis of CFS/ME can be made only after all other medical and psychiatric causes of chronic fatiguing illness have been excluded (Fukuda *et al.*, 1994). There is mounting pathological evidence from more recent studies for elevated ribonuclease L enzymic activity (Tiev *et al.*, 2003; Snell *et al.*, 2002) and decreased levels of the immune regulating endogenous opioid, beta-endorphin in peripheral blood mononuclear cells (Panerai *et al.*, 2002). New research has found

significant pathological disturbances in CFS/ME subjects such as reduction of membrane NA+-K+ ATPase activity, reduced serum magnesium, increased levels of tryptophan catabolites such as nicotine, altered levels of hypothalamic digoxin and other disturbed neuro-chemical and immune pathways (Georgiades *et al.*, 2003). Microbial flora have shown to be demonstrably altered in CFS/ME and there is much pathological evidence to indicate that these patients are subjected to increased oxidative stress, have increased type 2 helper cell cytokines, altered levels of essential fatty acid and malabsorption of certain nutrients (Logan *et al.*, 2003).

Simpson (1989) and Spurgin (1995) have studied red blood cell structure in various diseases and showed that the most common aberrant shape of a red blood cell in CFS/ME patients is a flattened disc with up to 80% of cells having this abnormal shape. This alteration may lead to loss of fluidity and flexibility of the RBC membrane resulting in reduced access of these cells to the deep capillary beds reducing oxygen supply to tissues exacerbating any fatigue. Decreased concentrations of essential fatty acids (EFA) in red cell membranes of CFS patients were thought to be causing the malformation of the erythrocytes. Recent research analyzing the essential fatty acid content in the blood found that the levels of the EFA arachidonic acid (ARA) and docosahexanoic acid (DHA) were decreased in patients suffering from CFS. However, the levels of the palmitic acid and oleic acid in the same lipid analysis were found to be increased which questions the aetiological relevance of the above finding (Liu *et al.*, 2003).

CFS/ME is not only restricted to man. Blood in animals presenting with symptoms of CFS/ME has been shown to contain micrococci-like organisms with positive staphylococci blood cultures. 80% of CFS/ME patients were shown to have micrococci in their blood especially if they were in constant contact with animals (Tarello, 2001).

Considerable evidence now indicates that the central nervous system is profoundly involved in the pathogenesis of CFS/ME (Georgiades *et al.*, 2003). What is also increasingly evident is that many research studies are now focussing on the high levels of toxicity found in CFS/ME patients such as organic solvents causing autonomic dysfunction

or heavy metals such as mercury that have neurotoxic properties ( Hokama *et al.*, 2003; Smith and Sullivan, 2003; Hotopf *et al.*, 2000; Shaheen, 2000 ).

Thus a significant number of distinct possibilities have emerged as being important in the development of CFS/ME. The areas of particular importance and relevance to the present work are reviewed in more detail in the following sections.

## 1.5 Causes and treatment of CFS/ME

Numerous suggestions have been made concerning the cause for the disorder. A rational classification is difficult because of the extensive overlaps between the different areas. Furthermore several theories have been developed largely from the apparent success of some therapies and therefore the possible causes and treatments are considered together in the following sections. There are, moreover, great difficulties in accurately defining the significance of psychological terms such as stress in a physiological context. Not surprisingly there has been much debate concerning the immunological, psychological and hormonal aspects. Nevertheless there is now available considerable data regarding these areas as well as the toxicological associations. The relevant information is reviewed in the following sections.

### 1.5.1 Immunological

The body provides two forms of specific adaptive immunity: Humoral and Cellular (Cell-mediated). Both are co-ordinated by the cells of the immune system and their mediators.

#### 1.5.1.1 Humoral immunity

Humoral immunity is the major defence mechanism against bacterial infections and utilises circulating antibodies that are produced by specialised cells, B-cells, supported by other cells called T-helper/inducer cells. After recognising foreign material B-cells multiply rapidly and produce antibodies comprised of large immunoglobulins. These protein molecules are produced in large numbers and are usually specific to the infective or foreign agent. The antibodies form complexes with the foreign material and these complexes are then destroyed by other cells, such as macrophages. A particularly important

immunoglobulin is secretory IgA (sIgA) which is secreted at mucous membranes, e.g., gut, lungs, etc, where it is a major barrier to pathogenic organisms (Bai *et al.*, 2004)

### 1.5.1.2 Cellular (cell-mediated) immunity

Cellular immunity involves a variety of T-cells that are responsible for protection against viruses, cancers, and some disease-causing bacteria such as tuberculosis. T-helper (Th) cells assist B-cells in mounting a humoral response and cytotoxic T lymphocytes (Tc) can actively destroy abnormal cells in disease and malignancies. A further group of cells are natural killer (NK), cells, which also play an important role in counteracting viral infections and cancer.

The complex interactions between all the B and T-cells require cytokines which are large protein signalling molecules. There are many types of cytokines which are subdivided into smaller groups (e.g. interleukins and interferons). During an infection both T and B-cells multiply rapidly with cell numbers returning to normal levels after the antigen has been defeated. However some memory cells remain so that a second infection is more rapidly combated. Some recent research findings have demonstrated a cytokine involvement in the pathophysiological mechanisms found in CFS/ME. The underlying immune activation results in a Th2-type response with significantly increased levels of T-cells producing interferon-gamma or interleukin-4 (type 2) (Skowera *et al.*, 2004).

### 1.5.1.3 The inflammatory response

This is a complex response to local injury or trauma and although it is usually acute there are a number of chronic inflammatory diseases that are well known such as rheumatoid arthritis and sinusitis. The inflammatory response also involves cytokines plus other classes of inflammatory modulators such as the prostaglandins.

The recent controversy about the role of the MMR (measles, mumps and rubella) vaccine being associated with the development of autism involved the identification of grossly inflamed lymphoid tissue in the lower part of the small intestine (Wakefield *et al.*, 2002). Inflammation of this part of the gut is common among CFS/ME patients and many have been diagnosed with irritable bowel syndrome, inflammatory bowel disease, and Crohn's

disease. Allergic reactions to food containing gluten are common. The best known of these is coeliac disease in which the structure of the small bowel is destroyed, with a flattening of the deeply folded villi of the gut wall, and a loss of the capacity to properly absorb many key food components. Generally CFS/ME patients do not test positive for coeliac disease but many become sensitive to many chemicals and foodstuffs, especially gluten (Logan and Wong, 2001).

When digestion is impaired then the larger peptide fragments are not broken down. Among these are opioid peptides derived from two principal sources, casein in milk (the casomorphins) and gliadin in gluten (the gliadomorphins) which occurs in wheat and related cereal crops. Opioids are peptides that have been found to possess morphine-like activity and are known to be naturally occurring in important transmitter molecules, particularly, in the gut, brain and immune system.

When the gut wall has increased permeability, these opioid peptides, which would normally be excluded, are absorbed and act both locally in the gut and in other organs, particularly the brain. The same factors that render the gut permeable also appear to increase the permeability of the blood-brain barrier and allow access of these compounds to the brain (Gershon, 1999; Hooper, 2003).

Depending on the concentration of opioids in the gut, as well as permeability of the gut and blood-brain barrier, then the overall level of these compounds in the bloodstream and the brain may vary and give rise to variable expressions of symptoms and dysfunction. Opioids also play a significant role in the immune response through receptors found on cells of the immune system. Generally they suppress the immune response and increase susceptibility to infection (Hooper, 2003)

The gut and the brain also communicate via messenger molecules generated by the immune response. There are receptors on brain cells for interleukins e.g. IL-1 (Dantzer, 2004).

Many symptoms associated with CFS/ME such as enlarged lymph glands, fever, gut symptoms, recurrent infections and non-exudative pharyngitis appear to indicate an immunological disorder. Indeed the onset of the disease often follows a viral infection. As reviewed below, many treatment approaches have been of an antiviral nature (Lerner *et al.*, 2002; Agut and Aubin, 1994; Blondel-Hill and Shafran, 1993). Some infections do cause long term fatigue. Patients exposed to Q fever (*Coxiella burnetii* infection) may develop chronic fatigue. Research determined that subjects involved in the West Midlands Q fever outbreak of 1989 had increased fatigue, compared to non-exposed controls 10 years after exposure (Wildman *et al.*, 2002). More serious pathology may be also linked to the pathogenesis of CFS/ME. A subset of disease-free breast cancer patients complained of a level of symptoms almost identical to CFS/ME sufferers, such as fatigue, sleep and loss of concentration (Servaes *et al.*, 2002). In an earlier study the fact that CFS/ME anecdotally had been linked with incidences of lymphoid hyperplasia and malignancy was examined. In Nevada (U.S.A.), patterns of Non-Hodgkin's Lymphoma were seen in a group of CFS/ME patients between 1984 and 1988. The researchers concluded however that there was no significant correlation between the incidence of malignancy and CFS/ME (Levine *et al.*, 1992). However a previous link was made between Non-Hodgkin's lymphomas and CFS/ME after an epidemiological investigation into a cluster of CFS/ME sufferers in North Carolina (Eby *et al.*, 1988).

### 1.5.1.4 Rnase L

A recent study has further confirmed the existence high levels of low molecular weight 2-5A binding polypeptide of 2-5A dependent ribonuclease L (Rnase L), generated by an increased proteolytic activity (Demettre *et al.*, 2002). Snell and co-workers discovered that increase in Rnase L enzyme activity may be linked to the low exercise tolerance and functional impairment found in CFS/ME. They suggest that both exercise testing and the Rnase L biomarker may be potential aids in the diagnosis of CFS (Snell *et al.*, 2002).

This disturbance in the 2-5A synthetase/RnaseL pathway and findings of abnormalities in T-cell subsets, IgG subset deficiencies and reduced natural killer cell activity plus increased delayed type hypersensitivity responses all support the hypothesis that CFS/ME is a disease

affecting the immune system (Shepherd, 1998). However in another study at the University of Glasgow, Rnase L pathway activation in the group of patients with acute gastroenteritis differed significantly from that of a healthy group and a group with CFS/ME, in whom there was no evidence of upregulation. This study strongly suggests that an assay of Rnase L antiviral pathway activation is unlikely to form a rational basis for a diagnostic test for CFS/ME (Gow *et al.*, 2001).

Chronic, low level immune activation leads to an overproduction of inflammatory mediators including cytokines which may lead to many of the symptoms of CFS/ME. Cytokines can bind to receptor sites within neurones mediating their effects. Studies by Suhadolnik and co-workers (1997 and 1999) have demonstrated upregulation of the 2-5A synthetase/RnaseL antiviral pathways in CFS/ME, signifying ongoing stimulation of T-type immune cells by interferons, viruses or other factors. Upregulation of these pathways can also be induced by chemical exposure (Vojdani, 1998).

Lloyd *et al.*, (1991) showed that disturbances in cellular immunity are factors in pathogenesis and response to treatment. 5mg of low-dose hydrocortisone treatment for CFS/ME has been shown to reduce the fatigue and also to reduce the level of disability (Cleare *et al.*, 1995), although there was a significant decline in improvement when the treatment ended. The symptoms and signs of CFS/ME are very similar to Addison's disease (primary adrenal insufficiency). However corticosteroid replacement where there are no physical signs of adrenal compromise is clearly unwarrantable as it would further exacerbate symptoms (Baschetti, 1998). In fact the only physical sign clinically identified by the author of adrenal dysfunction in CFS/ME is one usually attributed to high levels of cortisol, namely striae gravida (stretch marks) seen in Cushing's syndrome.

#### 1.5.1.5 Cytokines

Cytokines have an important role in regulation of the immune system (Maier *et al.*, 1998) which exerts numerous effects on autonomic function via the hypothalamus. Exposure to toxins, as well as infections, stimulates cytokine release (Reichlin 1993). There is also increasing evidence that exposure to emotionally stressful events induces cytokine release

and these mediate the neuroendocrine, neurochemical and behavioural effects of emotional stress. Cytokines stimulate the release of a number of neurotransmitters including noradrenalin acetylcholine, and serotonin. The cytokine interleukin -1 can stimulate hypothalamic release of CRH. Activation of CRH in turn stimulates noradrenalin release by increasing the availability of the enzyme tyrosine hydroxylase (Black, 1994).

There is also evidence of another way by which immune cells can communicate with the central nervous system. Lymphocytes have been shown to be capable of synthesising anterior pituitary hormones such as growth hormone and ACTH (Glaser and Kiecolt-Glaser, 1998) and small amounts of neurotransmitters, neurohormones and neuropeptides (Black, 1994). It has been proposed that viral or other infectious agents can directly and indirectly affect the regions of the brain that connect with the limbic system. Goldstein (1993) hypothesises that the limbic system response to cytokines may be abnormal in CFS/ME. Specifically, he speculates whether CFS/ME might be associated with altered levels of IL-1 antagonists which could potentially alter neuro-immune interactions and that infection results in immune activation leading to disturbed regulation of the CNS, particularly in the temperolimbic area.

The limbic system performs many key functions: regulation of memory and learning, integration of affect and psychosocial events, modulation of drive, integration of behaviour and higher control of hypothalamic and autonomic function. According to Goldstein (1993) 'limbic encephalopathy' could potentially explain many symptoms that are associated with this illness. These include pain; chemical sensitivity; immunological, neuroendocrine, neuropsychological and autonomic dysfunction; allergies and sleep impairment. Limbic system involvement is also consistent with the fluctuating nature of symptoms, particularly the exacerbation of symptoms in response to a range of stressors. Alterations in the activity of NMDA receptors in this region could explain a very common symptom of CFS/ME, namely alcohol intolerance. In one study CFS/ME patients exposed to toxic factors, such as ciguatera poisoning, organochlorine pesticides or those found in Gulf War veterans, showed more severe dysfunction of the immune system compared with CFS/ME patients

not exposed to toxins, whereas all the patients in that trial had disturbances in hypothalamic function (Racciatti *et al.*, 2001).

A number of studies have shown that hypothalamic, pituitary and limbic system lesions can alter many aspects of immune function. Depending on location, both immunosuppressive and immune-enhancing effects of such lesions have been reported, including reductions in immune cell numbers, proliferative responses to mitogens, natural killer cell activity and antibody responses (Ader *et al.*, 1995).

Data from a number of studies has shown that immunosuppression can be conditioned according to the principles of Pavlov. It has been repeatedly demonstrated that the pairing of an immunosuppresive drug with a sensory stimulus can eventually condition the subject to respond to the sensory stimulus alone with immunosuppression (Black, 1994). This demonstrates a strong interaction between the brain and the immune system.

As discussed further in section 1.5.8 the free radical nitric oxide has been shown to have neurotoxic properties. Reichlin (1993) proposes that in the CNS activated monocyte and glia can release nitric oxide, which exerts toxic effects via its ability to hyperstimulate glutamate receptors.

Detoxification systems in the liver play a key role in generalised stress response via their role in dealing with the metabolic products of stress (Sternberg *et al.*, 1992). The gut has an intricate immune system network, abundant autonomic innervation and produces a number of neurotransmitters. Lymphocytes in the gut secrete small amounts of hormones that are thought to play a local role in regulating inflammation in the gut (Reichlin 1993). It is possible that the release of hormones in the gut is influenced by stress. Indeed psychoneuroimmunomodulation is likely to contribute to the balance of gut function (Anisman *et al.*, 1996). It is conceivable, that with recognition of the importance of neuroimmune interactions, these impairments may be a result of disrupted communications in the neuroimmune network.

The immune system has been shown to exert numerous effects on the hypothalamus and thus the autonomic nervous system. Immune activation is associated with increased firing rate of hypothalamic neurones. Activated immune cells release cytokines that are important mediators of the stress response (Ader *et al.*, 1995). How cytokines reach and activate the central nervous system is still not fully understood (Watkins *et al.*, 1995). It is known that activated immune cells can cross the blood-brain barrier and release cytokines and other immune mediators into the central nervous system (Reichlin, 1993). Central and peripheral administration of cytokines impacts on a range of behaviours including feeding, sleeping, drinking, levels of activity and mood, presumably by their action on receptor sites in the limbic system. Infections have an effect on the limbic system which plays a major role in regulation of memory and learning, and is directly involved in hypothalamic and autonomic function. Dysfunction of the limbic system may lead to many of the symptoms associated with this illness and thus CFS/ME patients are very sensitive to both physical and psychological stress. Also functional changes in limbic areas have been demonstrated in CFS/ME using SPECT scans (Goldstein, 1993). The limbic system controls emotions and dream states and it is noteworthy that patients with CFS/ME often complain of mood swings and weird or extremely vivid dreams, nightmares or, in extreme cases, hallucinations.

In the acute stage of infection cytokines are responsible for fatigue, inactivity, anorexia and associated neuroendocrine and metabolic changes (Reichlin, 1993; Anisman *et al* 1996). Exposure to infection, toxins and injury has been shown to stimulate cytokine release (Reichlin, 1993). It is significant that interferons, when used medicinally, have been associated with neurological and psychiatric side effects (Morag *et al.*, 1998). There is also evidence that exposure to stressful events induces cytokine release. These cytokines mediate the neuroendocrine, neurochemical and behavioural effects of stress. The cytokine interleukin IL-1 inhibits neuronal secretion of acetylcholine (Reichlin, 1993), whereas some cytokines stimulate the release of acetylcholine and other neurotransmitters including noradrenalin, and serotonin. IL-1ra inhibits cytokine effects and thus inhibits these neurotransmitters (Reichlin, 1993). Cytokine IL-1 has been shown to stimulate hypothalamic release of corticotropin releasing hormone (CRH) which stimulates

noradrenalin release. There is also evidence that lymphocytes can synthesise neurotransmitters (Black, 1994).

### 1.5.1.6 Immunological therapies

An alternative term for CFS/ME in the USA is Chronic Fatigue Immune Deficiency Syndrome (CFIDS) recognising that dysfunction of the immune system is a major feature of this disease. Many immune modulatory treatments are expensive, not freely available and produce unpleasant side effects (Shepherd, 1998). The results of randomised controlled trials of immunoglobulin therapy have been contradictory (Hickie *et al.*, 1992; Uchida, 1992; Lloyd *et al.*, 1990; Matsuda J, 1992; Vollmer-Conna *et al.*, 1997).

## 1.5.2 Viruses and anti-viral therapy

Some viruses, known as enteroviruses such as the *Coxsackie* B group, are known to be particularly important in triggering CFS/ME (Richardson, 2001). Hence treatment approaches over the years have focussed on antiviral medications (Blondel-Hill and Shafran, 1993). Drugs such as acyclovir have been unsuccessfully tested on CFS/ME patients with abnormal Epstein-Barr virus (EBV) serology following glandular fever in a randomised controlled trial (Straus *et al.*, 1988). Patients treated with cytokine interferon α showed no significant improvement but some of them developed major side effects such as palpitations, worsened fatigue, flu-like symptoms, diarrhoea, hair loss and mild boils (See and Tilles, 1996). The Effect on cytokine levels of the oriental medicine Bojungikki-tang (BIT), which has been widely used in the Far East to treat CFS/ME, was investigated and showed a slightly lower inhibitory effect of LPS-induced Interferon (IFN)-gamma production. These results suggest that BIT may be useful in treating CFS/ME (Shin, 2003).

A subset of CFS/ME patients, all having significant IgG type human cytomegalovirus titres, showed significant improvement following treatment with the antiviral agent ganciclovir (Agut and Aubin, 1994). Lerner *et al.*, (2002) later showed that another anti-viral drug valacyclovir was successful in improving cardiac function in CFS/ME patients who were initially infected by the Epstein-Barr virus.

It has been shown in some CFS/ME patients that there is an up-regulation of 2-5A synthetase/RnaseL pathway which is involved in the normal defence against viruses (Suhadolnik *et al.*, 1997). Poly (1)-poly (C12U), better known as ampligen (a synthetic, mismatched double-stranded RNA), has potent anti-viral and regulatory properties, and came to prominence in the 1980's when it was billed as a potential cure for AIDS. In trials baseline RnaseL levels were significantly reduced in the treatment group but not in the placebo group (Cotton, 1991). In view of the mode of action of ampligen, there is a potential risk that it could interfere with genetic material in the cell. For this reason it has not received approval for treatment of this condition in the USA, Europe or in the UK.

## 1.5.3 Allergies and sensitivities

Studies of the part played by allergies in CFS/ME have shown that they cause chemical and food sensitivities (Straus, 1994; Bell *et al.*, 1998), with many cases of hypoergy or anergy reported (Lloyd *et al.*, 1988). Excessive N-methyl-D-aspartate (NMDA) receptor activity has been implicated in multiple-chemical sensitivity brought on by previous exposure to hydrophobic organic solvents or pesticides (Pall and Satterlee, 2001). Some CFS/ME patients, with high levels of sensitivity bordering on allergy, have been treated by Miller neutralisation. The latter involves provocation of the skin or sublingual mucosa followed by the administration of a neutralisation 'vaccine' of individual allergens. It acts by stimulating the body to produce higher levels of detoxification enzymes, thus helping the body cope with the allergen (Miller, 1987). Enzyme-potentiated desensitisation (EPD) is another anti-allergy treatment that clinically has benefited many CFS/ME patients by actively adding enzymes to enhance the desensitising effect and is applied to a scratch in the skin or can be given by intradermal injection (Fell and Brostoff 1990).

## 1.5.4 Hormonal imbalances

Since the hypothalamus is the principal coordinator of hormonal secretion, hypothalamic dysfunction in CFS/ME, proposed in this thesis, will likely affect the entire endocrine system and thus one might find excesses or deficiencies in many hormonal levels in patients with this disease. Both raised (Scott and Dinan, 1999) and reduced (Kuratsune *et al.*, 1998) levels of a precursor of the major sex hormones serum dehydroepiandrosterone

(DHEA-S), secreted from the adrenal glands, have been found in CFS/ME. As with many hormones, both high and low levels of melatonin, produced by the pineal gland, have been reported in a sample of patients with CFS/ME (Knook *et al.*, 2000; Sterzl *et al.*, 1998). Melatonin levels are found to be high when day-time drowsiness and excess sleep are reported. However when insomnia is a major symptom, supplements of melatonin are usually beneficial (Shepherd, 1998).

Reduction of insulin-like growth factor (IGF-1), the main mediator of growth hormone effects, is also found in CFS/ME. Hypoglycaemia, often found in CFS/ME, stimulates the hypothalamus to reduce the growth hormone level (Allain *et al.*, 1997).

### 1.5.4.1 Corticotropin releasing hormone (CRH)

Corticosteroids have immunosuppresssive, antiallergenic and anti-inflammatory effects. During the stress response increased levels of circulating cortisol ensure that several aspects of immune function are restrained (Ader *et al.*, 1991). The restraining effect of corticosteroid on immune function is achieved via a negative feedback loop. They inhibit cytokine synthesis at a genetic level (Maier *et al.*, 1994). This is associated with the inhibition of general functions such as growth, reproduction and thyroid function in response to stress (Black, 1994).

Data from a number of studies suggests that both primary and secondary lymphoid tissues are innervated by the sympathetic nervous system. This is evidence of a direct neural link between the SNS and the immune system and suggests that activation of the sympathetic nervous system can directly influence immune cell function (Black, 1994). Activation of the SNS leads to increased catecholamine release, which is associated with increased leukocytosis, increased lymphopenia and reduces natural killer cell activity. There is also substantial evidence for neural connections between autonomic nuclei in the noradrenalin-producing locus coeruleus of the brain stem and the paraventricular nucleus of the hypothalamus. Indeed it has been shown that neurones in the locus coeruleus have receptors for CRH. The noradrenalin produced by noradrenergic neurones in the locus coeruleus and CRH participate in a positive feedback loop, with each system reinforcing the function of

the other (Sternberg *et al.*, 1992) Glucocorticoids, ACTH, and CRH itself exert negative feedback controls on the production of CRH and noradrenalin.

Corticotropin Releasing Hormone (CRH) and noradrenalin are thus thought to have a central role in precipitating the generalised stress response. Some studies indicate that neurotransmitters including acetylcholine, serotonin, and noradrenalin can mediate much of the neurogenic stimulation of CRH production (Black, 1994). Serotoninergic neurotransmission is activated in response to stress. It has also been shown that glucocorticoids can influence serotonin levels by altering receptor density or regulating synthesising enzymes (Herbert, 1997). The immune system has been shown via chemical mediators to have distant effects on the central nervous system, particularly the HPA axis, the limbic system and autonomic nuclei (Sternberg *et al.*, 1992). The salivary cortisol response to awakening is used as a non-invasive test of the capacity of the HPA axis to respond to stress. Measuring salivary cortisol in 56 patients with CFS/ME comparing them with 35 healthy controls the HPA axis response to stress in CFS/ME was shown to be significantly impaired (Roberts *et al.*, 2004). Even depression is sometimes associated with hypercortisolaemia and reduced serotoninergic function (Herbert, 1997).

It has been proposed that CRH may be the key co-ordinator of the stress response in humans (Dunne and Berridge, 1990). These workers have shown that arousal pathways are activated in response to stressful external stimuli leading to activation of neurones in the paraventricular nucleus of the hypothalamus. Stimulation of CRH neurones leads to increased CRH release. It has been shown that psychological stress can upregulate the expression of CRH, thereby activating the HPA axis.

There is growing evidence to suggest that the brain responds to stress through alterations in the expression of immediate-early genes in the hypothalamus, the brain stem, the amygdala, monoaminergic and autonomic nuclei (Herbert, 1997). In circumstances of repeated stress, patterns of gene expression can change. Herbert (1997) proposes that these immediate-early genes play a role in the regulation of the expression of later genes, which determine peptide synthesis and receptor expression. This may explain how stress can alter the levels of

neurotransmitters and can up or down-regulate receptors for hormones and neurotransmitters. Acute stress has been shown to be associated with increased levels of CRH produced by the hypothalamus and consequent increases in levels of ACTH and cortisol. Cortisol has important immunomodulatory effects, but it is only one of many immunomodulators. The production of all of the pituitary hormones is influenced by stress. Some are immunoinhibitory such as glucocorticoids and ACTH whilst others are immunostimulatory including growth hormone, prolactin, and CRH (Reichlin, 1993). The release of growth hormone and prolactin is initially activated during the stress response but this is later inhibited by alterations in the levels of neurotransmitters such as dopamine in the case of prolactin (Black, 1994). Data from a number of studies shows that exposure to recurrent or chronic stress can result in a lowering of growth hormone and prolactin levels. As immune cells contain receptors for these hormones, alterations in their levels are likely to have consequences for immune activity. Levels of dopamine and opioids, particularly ß-endorphins, increase during the generalised stress response. Immune cells have been shown to hold receptors for various neurotransmitters, neuropeptides and neurohormones. Noradrenalin can act at receptor sites on lymphocytes and macrophages inhibiting mitogenesis and complement activation, increasing the expression of cell surface antigens and antibody responses. The neuropeptide substance P can bind to receptors on lymphocytes enhancing lymphocyte migration to sites of inflammation, and lymphocyte production of IgA (Ader *et al.*, 1995).

### 1.5.4.2 Hormone therapy

Since growth hormone deficiency leads to symptoms similar to those of CFS/ME, growth hormone has been used in the treatment of CFS/ME patients (Bennett *et al.*, 1998), showing a significant reduction of symptoms after six months in the experimental group compared with the control group of patients treated with a placebo. However the improvement was short lived after therapy was discontinued.

## 1.5.5 Depression and anti-depressant treatments

It has been stated that two out of three patients in primary care with CFS/ME have co-morbid psychiatric disorders (Wesseley, 1997), with major depression being partially common.

Antidepressant drugs have been used for symptomatic relief in many non-psychiatric illnesses such as Parkinson's disease, multiple sclerosis, hypothyroidism and even in cases of brain tumours (Lynch *et al.*, 1991). Likewise they can sometimes reduce the symptoms of CFS/ME (Lynch *et al.*, 1991, Wilson *et al.*, 1994). However symptomatic improvement occurs at much lower doses and more rapidly than in depression (Wilson *et al.*, 1994, Natelson *et al.*, 1996).

In addition to the use of antidepressants to lessen the symptoms of anxiety and depression in CFS/ME they have been shown to alleviate sleep disturbances (Klonoff, 1992) and decrease pain perception. Occasionally symptoms of depression in CFS/ME may be severe enough to require antidepressant therapy (Lynch *et al.*, 1991) which was shown to have a low placebo effect (Natelson *et al.*, 1996). However the patients in these cases may have two distinct co-morbid conditions.

Insomnia and hypersomnia have been validated via polysomnography techniques as symptoms of CFS/ME and not due to a co-morbid psychiatric condition (Stores *et al.*, 1998). Low doses of tricyclic antidepressants such as amitryptiline are frequently prescribed to aid a return to a normal sleeping pattern. Many patients with CFS/ME who find it difficult to 'switch off' when trying to fall asleep are regularly advised to take 10 to 25 mg of amitryptiline one hour before retiring to bed. This is significantly less than the normal dose of this mild tricyclic antidepressant, which when prescribed for anxiety/depression would normally be 75 mg twice a day. Many patients with CFS/ME cannot endure the effects of antidepressants, thus dropout rates from studies into antidepressant therapy in CFS/ME exceed those of patients with depression (Natelson 1996; Vercoulen *et al.*, 1996).

## 1.5.6 The role of toxins in the pathogenesis of CFS/ME

The term toxin was originally coined in the late nineteenth century and is defined as an antigenic poison or venom of plant or animal origin, especially one produced or derived from micro-organisms and causing disease when present at low concentrations in the body (The New Oxford Dictionary of English, 2001). To allow semantic simplicity "toxin" is used in this work in the broader sense of any substance harmful to the body. For instance mercury, which is a heavy metal toxin, is neither from plant or animal source but it still is a major "toxin" to the body.

This section will review evidence that CFS/ME is one of many syndromes which can be caused by the breakdown in the detoxifying mechanisms in the body especially within the central nervous system. Further references will present evidence supporting the hypothesis that impairment of drainage of toxins via the CSF-lymphatic pathway from the neuraxis (Cserr and Knopf, 1992) is a major factor in the pathogenesis of this disorder.

### 1.5.6.1 Pollutants

Environmental pollutants have long been seen as predominant aetiological factors in neurodegenerative disease, although there are also very probably genetically determined susceptibilities ( Johnson, Hodge and Duvoisin, 1990) Studies have revealed major variations in individual ability to detoxify noxious agents and shown that neurological disease may derive from an exceptional vulnerability to certain neurotoxins from both external sources in the environment and from toxic free radicals and/or excitatory amino acids normally found within the central nervous system (Calne *et al.*, 1992.)

Over 60,000 chemicals were identified in the 1990's as known or potential toxic substances by the United States environmental protection agency (Veronesi, 1992). The U.S. Government Office of Technology estimated that up to 25% of all chemicals may be neurotoxic (Tilson and Mitchell, 1992). Each year approximately 1000 new chemicals are produced and no matter what safety procedures are taken they all are inadvertently or deliberately introduced into the environment via air or water or in our food (Sabljic *et al.*,

1991). There are 8 basic sources of toxic exposure and most of the following have been implicated as potential aetiological factors of CFS/ME:

1. Air Pollutants (indoor and outdoor) such as benzene and chloroform. These may originate from domestic fires: e.g. CFCs, PCBs or automobile-related activities: e.g. carbon monoxide and toluene and obviously in tobacco smoke: e.g. nicotine
2. Food Contaminants and Additives: e.g. caffeine and saccharin.
3. Water Pollutants: e.g. chlordane and toluene. Most water supplies contain toxic amounts of heavy metals e.g. mercury and aluminium (Gardner and Comber, 2003; Kazantis, 2002)
4. Soil Contaminants: e.g. lindane some of which may arise from domestic garden and lawn activities: e.g. aldrin and dieldrin, including pesticides such as DDT and other organophosphates.
5. Hobbies and Crafts: e.g. formaldehyde; trichloroethane.
6. Household Activities: e.g. ammonia; fluoride.
7. Accidental Spills: e.g. truck accidents or pipeline ruptures.
8. Workplace contaminants such as solvents or radioactive substances.

Toxic chemical exposure can cause many serious conditions including cardiovascular, kidney or endocrine diseases, depression and even psychosis (Rea, 1993). Many different neurotoxins have been implicated in the pathogenesis of CFS/ME including organophosphates and mercury (Gimenez *et al.*, 1999). As early as 1961 chronic fatigue was seen as a major symptom following chronic exposure to organophosphates (Gershon and Shaw, 1961), so it is of no surprise that levels of serum organochlorides have been found to be higher in CFS/ME patients compared with normal subjects (Dunstan *et al.*, 1995). Aerosol propellants found in hair spray, deodorants and spray paints contain high levels of methylene chloride which when inhaled affects the brain and liver causing symptoms such as fatigue, lethargy, headaches and chest pain. Analysis of the breath in residents in a New Jersey suburb revealed traces of many toxic compounds including chloroform, benzene, carbon tetrachloride, trichlorethane and many other harmful pollutants (Wallace *et al.*, 1986).

### 1.5.6.2 Effects of neurotoxins

The most common organ affected by toxins is the brain leading to fatigue, exhaustion, cognitive impairment, loss of memory, insomnia and sleep apnea and other disturbing symptoms (Rogers, 1990). As mentioned above, toxic chemical exposure can cause many serious conditions including cardiovascular, kidney or endocrine diseases, depression and even psychosis (Rea, 1993).

There are several specialised regions of the brain's ventricular system, termed circumventricular organs, which interact closely with the CSF. These zones, for example the area postrema in the fourth ventricle, are chemical sensitive regions that may react with toxins sending messages to other parts of the brain. One important circumventricular organ is the cup-shaped lamina terminalis situated at the rostral end of the third ventricle projecting around the ventricle into the hypothalamus. In inflammatory or infective disorders cytokines such as IL-1 have been shown to pass through to the hypothalamus via the lamina terminalis raising the body's temperature. Also, one of the most permeable regions of the blood brain barrier is at the hypothalamus facilitating its ability to the monitor hormone level in blood. This increased permeability also makes the hypothalamus one of the most prone regions in the brain to suffer a toxic insult.

In the central nervous system there are several populations of electrically inexcitable cells that are known collectively as glia. Since glia are highly interactive with neurones they are potentially critical as targets and mediators of neurotoxicity, (Lopachin and Aschner, 1993). The class of glial cells termed astrocytes are capable of phagocytic activity (Iacono, *et al.*, 1991; Lindo, *et al.*, 1993; Noske, *et al.*, 1982) as are microglia (Perry and Gordon, 1988). This capacity is involved in the remodelling of synapses during development but also may be used for engulfing foreign material and is essential in the brain's defence against neurotoxins. Glia are also known to produce and respond to cytokines and related molecules (Morganti-Kossman, *et al.*, 1992; McMillan, *et al.*, 1994). Certain cytokines, such as IL-1 and INF-γ, stimulate astrocytes to proliferate and release further cytokines (Benveniste, 1993; Suzumura, *et al.*, 1993; Yong, 1992). Others may have down-regulatory effects: for example, Lindholm and colleagues (1992) have demonstrated that transforming

growth factor-*B*1 can inhibit astrocyte proliferation as well as simultaneously increasing secretion of nerve growth factor (Sawada, *et al.*, 1993).

Clinically CFS/ME resembles the symptoms of chronic ciguatera fish poisoning (CCFP). These similarities suggested the exploration of lipids in sera of CFS/ME, CCFP, and other diseases with the membrane immunobead assay (MIA), which is typically used for screening ciguateric ocean fish. In a recent study using the MIA to examine lipids in sera of CFS/ME, 95.6% of the patient group had greater or equal to 1:40 titre with a significant increase ($P<0.001$) in chronic phase lipids (CPLs) relative to a healthy normal group (Hokama *et al.*, 2003).

Autonomic dysfunction has long been associated with many toxic substances especially following exposure to organic solvents, with some exhibiting symptoms of peripheral neuropathy (Matikainen. and Juntunen, 1985).

Under normal conditions, the blood-brain barrier protects the CNS from rapid fluctuations in levels of ions, neurotransmitters, bacterial toxins, growth factors and other substances. The permeability of the blood-brain barrier to the acetylcholinestease inhibitor pyridostigmine has been shown to be enhanced by stress (Hanin, 1996).

Each organ or tissue may act as a discrete target for some toxic substances which may lead to dysfunction of the whole organism. Specific molecules within a particular cell type act as primary targets. Neurotoxicology is extremely complicated due to the diverse nature of its cellular and biochemical composition (Cookson, 1995). For example, biochemical specialisations of differentiated neurons lead to varied susceptibility to neurotoxicants. Some neurons are less susceptible to toxic damage (e.g., serotonergic neurons) leading to regions of the brain that are not as sensitive to toxins (Langston *et al.*, 1983). Dopaminergic neurons, conversely, are particularly sensitive especially to the toxicant MPTP (1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridinium). This leads to a loss of neuronal function in the substantia nigra, where these neurons are concentrated, leading to Parkinsonism

(O'Callaghan, 1991). Inhibition of mitochondrial oxidation, resulting in ATP depletion, has been found after toxic exposure to MPTP in Parkinson's disease (Langston *et al.*, 1983).

An increase of choline has been found in the occipital cortex of CFS/ME sufferers (Puri, *et al.*, 2002). Excess breakdown in acetylcholine could lead to high levels of choline in the brain. Organophosphates irreversibly inhibit the action of acetyl-cholinesterases at muscarinic and nicotinic synapses leading to a surplus of acetylcholine (Ellenhorn, 1997).

Cholinergic dysfunction has been suggested as a primary aetiology in CFS/ME. A hyperactive peripheral cholinergic vascular response, vascular endothelial cell dysfunction, chronic inflammation and apoptosis have been noted in organophosphate exposed patients and patients who served in the first Gulf War (Spence *et al.*, 2000).

### 1.5.6.3 Mercury poisoning

The doses of neurotoxins required to produce behavioural and or sensory dysfunctions are low and may also be cumulative, such as with methylmercury exposure in adult humans (Weiss, 1988). The nervous system may also be particularly vulnerable during development. Toxicants such as ethanol may exert greatest effect *in utero* whilst others, such as lead, produce IQ defects in children (Needleman *et al.*, 1990). It has also been suggested that heavy metal toxins pass through to the infant via ingested mother's milk and that higher concentrations of toxicity transfer to the older child particularly the firstborn if breast-fed (Drasch *et al.*, 1998; Drasch and Roider, 1995; Drasch *et al.*, 1994).

Mercury has been implicated as a major heavy metal neurotoxin to affect the body leading to neurological dysfunction and oxidative stress (Sarafian and Verity, 1991). A primary source of mercury poisoning is the amalgam in dental fillings (Mutter *et al.*, 2004). Heavy metals also transfer from expectant mothers to their children, with first born being more affected by this "dumping ground" of mercury (Drasch and Roider, 1995).

Mercury is also present in the preservative thiomersal, a major component of vaccinations. Long before the questions raised by MMR, various vaccinations have been implicated as

aetiological factors of CFS/ME. Aluminium has been also shown, like mercury, to exert neuro-toxic effects (Garrel *et al.*, 1994).

### 1.5.6.4 Diet and toxicity

Exposure to chemicals will affect people in different ways depending on the status of several factors. Diet plays a pivotal role in the body's ability to withstand toxicity. Toxins can be produced from non-toxic foods that we eat, building up in the central nervous system, liver or kidneys. Sugar may not be broken down correctly when energy is required leading to brain and muscle fatigue and many other symptoms.

Trace elements often used as supplements for prompting good health may become toxic if ingested in too high a dose. Selenium may be taken up from the soil by certain plants such as species of the *Astralagus* genus in sufficient quantities to render them toxic. Chronic selenium poisoning in animals, known as Alkali Disease, leads to livestock presenting with lameness, depressed appetite, lack of vitality, hair loss and emaciation (Witte *et al.*, 1993).

Healthy food may not be properly digested or absorbed. A leaky gut due to the insult of the intestinal wall may be present leading to semi-digested food entering the blood stream causing immune responses propagating further toxicity. This has been the focus of recent interest (Schwarz *et al.*, 1999; White, 2003).

Damage of the lining of the alimentary canal may be caused by a variety of irritants, most common being alcohol, aspirin, gluten and *Candida albicans* (Burke and Gracey 1980). Deficiencies in some vitamins, proteins, essential fatty acids and minerals are also known to lead to poor intestinal cell growth causing increased permeability of the gut wall (Schumann, 2001).

### 1.5.6.5 Vaccinations and Gulf War syndrome

Vaccines are clearly associated with Gulf War Syndrome/illness which shares many similar symptoms with CFS/ME (Hotopf *et al.*, 2000; Shaheen, 2000). Central as well as peripheral nervous system dysfunction occurred in veterans of the first Gulf War (GWVs) who were

exposed to both chemical and severe psychological war stresses (Hooper, 1999; Nicolson, 1998). However environmental factors could be responsible for some of the complaints of GWVs (Haley and Kurt, 1997). Exposure to pesticides (particularly organophosphates), oil and smoke from the oil well fires, depleted uranium, chemical weapons, as well as vaccines, could all have contributed to the many cases of acute and chronic respiratory illnesses reported in GWVs. In fact as many as 70% of those receiving two or more vaccines given simultaneously during deployment showed symptoms of acute or chronic respiratory illnesses. The war to free Kuwait from the invading forces of Iraq has been described as the most toxic war in Western Military History, with at least 14% of US GWVs fulfilling the CDC criteria of chronic fatigue syndrome (Hooper, 2000).

A further important conclusion from research on GWVs is that post-traumatic stress disorder is not a major factor and any soldiers diagnosed with this psychological disorder were mostly ill before deployment at the time when vaccinations were at their highest level. In fact occurrences of post-traumatic stress disorder lessened during deployment. This throws doubt on any suggestion that GWVs are simply suffering from a psychiatric War Syndrome (Unwin *et al.*, 1999; Ismail *et al.*, 1999; Jones and Wessley, 1999; Hyams *et al.*, 1996)

Other studies offer further evidence of vaccination linked toxicity found in GWVs. *Mycoplasma* infections were three times more likely to occur in non deployed vaccinated GWVs than in veterans not vaccinated (Steele, 2000). It was hypothesised by the researchers that gene-modified *Mycoplasma* could have come from an experimental HIV vaccine or from a biological weapon leading to extensive contamination of Coalition Forces. *Mycoplasma*s have the potential to act as super-antigens thereby triggering a range of autoimmune diseases. The transmission to other family members has been demonstrated to involve *Mycoplasma.* Autism and Autism-related Disorders have been found in children born to GWVs. Also many family members of GWVs have been diagnosed as suffering from CFS/ME with over 50% giving a positive result when tested for any species of *Mycoplasma,* with *Mycoplasma fermentans* being the most commonly found (Nicolson *et al.*, 2000).

### 1.5.6.6 Radiation

In the present era we are exposed to invisible agents as well as the more discernible. Radiation exposure can cause release of a range of toxic compounds in the damaged tissue. A survey on 11,000 Norwegians and Swedes found that many were suffering headaches and fatigue from using mobile phones. Risk of brain tumours in the temporal lobe has been shown to be increased by the use of the analogue cellular mobile phones on the same side as the tumour (Hardell *et al.*, 2002). Scientists working for the Radiation and Nuclear Safety Authority in Finland have found that exposing humans to one hour of mobile phone radiation affected the integrity of the blood-brain barrier leading to larger toxic molecules passing into the CSF, with the potential of causing damage to brain tissue (Leszczynski, 2001).

### 1.5.6.7 Predisposition to toxicity

Previous exposure of toxins will increase the sensitivity to further toxic insult. Genetically some people have a greater ability to detoxify and, unfortunately, some are much more likely to have worse symptoms from toxic causes due to hereditary predisposition. Likewise prior state of health, with emphasis on the immune system, will be a major significant factor to consider when assessing ability to withstand exposure to poisonous chemicals. Age is obviously important, with children much more susceptible to toxic overload than an adult, hence the smaller dosages of prescribed medicine allowed to children (Jett *et al.*, 1997).

Several toxic chemicals of low-molecular weight have the potential to induce autoimmune diseases such as Systemic Lupus Erythematosus (SLE) (Kammuller, *et al.*, 1989, Rogers, 1990; Tilson and Mitchell, 1992; Offit *et al.*, 2004). This adds support to the theory of Itoh *et al.* (1999) which proposes that the immune system changes in CFS/ME are likely to render individuals prone to autoimmune attack. Genetic susceptibilities for immune expression have been discovered in diseases such as autoimmune hepatitis (Czaja and Donaldson, 2000) which may also be important determinants of susceptibility for a disease such as CFS/ME.

## 1.5.7 Diet and dietary therapies

### 1.5.7.1 Supplements

Many CFS/ME patients suffer from food intolerances. Dietary interventions involving low carbohydrate, gluten and yeast have been proposed. However, nutritionists at Harvard Medical School found that there is no clinical scientific research evidence to substantiate claims about the appropriateness and efficacy of various dietary approaches (Moriss and Stare, 1993). Vitamin and mineral supplements are widely recommended in the treatment of CFS/ME but there is no evidence that megadoses of vitamins and minerals will relieve any of the CFS/ME symptoms for which they are promoted. However the antioxidant action of vitamin C does improve the body's immune response. With patients taking no more than 500mg per day there have been no reported toxic side effects (see also section 1.58). Similarly the vitamin B group is known to aid the health of the nervous system. Functional deficiencies of the B vitamins pyridoxine, riboflavin and thiamine has been shown to occur in CFS/ME (Heap *et al.*, 1999) and thus patients are often advised to take one full and complete Vitamin B complex pill per day as long as no complications are reported.

Magnesium deficiency is associated with disorders of neuromuscular and psychiatric functioning. It also results in an inability to cope with viral infections (Werbach, 1998). In a randomised controlled trial of magnesium treatment in CFS/ME, Cox and colleagues (1991) found that the 20 patients they studied had significantly lower red blood cell magnesium levels compared with healthy controls. Werbach (1998) recommended taking a combination of magnesium and malic acid to aid production of ATP. The benefits of magnesium for CFS/ME were refuted in another paper (Russell *et al.*, 1995). Rude *et al.* (2004) found that in magnesium deficient rats, there were increases in the concentrations of proinflammatory cytokines and substance P. Also chronic stress and the associated enhanced catecholamine release can result in magnesium deficiency.

Deficiency of sodium can produce similar symptoms to CFS/ME and is associated with neurally mediated hypotension, which occurs frequently in CFS/ME (Werbach, 1998).

However the increase in salt intake that is occasionally advised may pose extreme danger for the many CFS/ME patients who suffer from concurrent hypertension.

Essential fatty acids are used in oxidative phosphorylation in the mitochondria of muscle and in neuronal metabolic processes. Disordered metabolism of fatty acids may play a role in CFS/ME, with patients receiving Efamol Marine showing significant improvement (Behan *et al.*, 1990).

### 1.5.7.2 Elimination and avoidance diets

Infection with the yeast *Candida albicans* can cause a chronic candidiasis hypersensitivity syndrome (CCHS) (Crook, 1984). Renfro and co-workers (1989) noted that the 'yeast connection' is frequently a condition that is self-diagnosed on the basis of having typical symptoms and a history of frequent yeast infections and multiple courses of antibiotics. Diets are available to eliminate the yeast *Candida albicans* by avoidance of foods on which *Candida* thrives. Low sugar diets are recommended as a means of combating *Candida* overgrowth, as yeast requires sugar for metabolism. There is no scientific evidence that such regimes actually control *Candida* overgrowth and these diets are nutritionally unbalanced which if followed for longer than 2 – 3 months could result in long-term nutritional deficiencies that may impair recovery.

### 1.5.7.3 NADH

Upregulation of the enzyme RNAseL and 2'-5' A synthetase has been observed which could lead to reduced levels of cellular ATP resulting in physical and cognitive fatigue. Depletion of ATP has been improved by supplementation with NADH (the reduced form of nicotinamide adenine dinucleotide) enhancing energy production at the cellular level (Forsyth *et al.*, 1999).

### 1.5.7.4 L-Carnitine

Histological and biochemical muscle abnormalities have been reported in some patients with CFS (Behan and Behan, 1988) and specifically mitochondrial abnormalities have been noted in a number of studies (Kuratsune *et al.*, 1994). L-carnitine is a product of two of the

essential amino acids that the body cannot produce on its own: lysine and methionine. L-carnitine is often referred to as a vitamin-like molecule because it is synthesized in the liver and kidneys from the amino acid lysine and other nutrients. At a basic cellular level, L-carnitine plays a critical role in the metabolism of fat, contributing to the oxidation of fatty acids and transporting long-chain fatty acids to the place in the cells (mitochondria) where they are processed to help provide energy, among other things. It is possible that L-carnitine deficiency could contribute to skeletal muscle symptoms.

L-carnitine levels are very difficult to measure and thus most studies focus on the derivative acylcarnitine. Periods of recovery from generalised fatigue were found to be associated with increases in serum acylcarnitine levels in the patients studied in a trial of L-carnitine therapy with CFS/ME (Plioplys and Plioplys, 1995).

## 1.5.8 Oxidative stress

Oxidative stress has been acknowledged as a common feature in many disease processes including CFS/ME. Oxidative stress may induce many of the symptoms of CFS/ME. Excessive production of the free radical nitric oxide could induce vascular, neurological, immunological, and muscular effects. Nitric oxide can be released in cells of the central nervous system which exerts neurotoxic effects by over-stimulating glutamate receptors (Reichlin, 1993). A free radical is a highly unstable and reactive molecule due to the loss of an electron from the shared covalent outer ring. It will damage the healthy tissue by trying to obtain another electron from an adjacent molecule. Oxygen reacts with free radicals to form peroxidised radicals which further insult healthy molecules. Oxidative stress increases free radical production leading to further cell damage and worsening toxicity. External factors such as environmental pollutants and radiation also can lead to major free radical production. Overall nitric oxide synthesis is increased in CFS/ME and may be induced by inflammatory cytokines (Pall, 2000). The neurotoxic affect is further aggravated by amplified sensitivity due to increased nitric oxide stimulation of the neurotransmitter glutamate (Pall and Saterlee, 2001).

The free radical nitric oxide has a positive function in aiding leukocytes to kill invading pathogens and also aids vascular tone. The most common free radical naturally produced in the body is superoxide derived from oxidative phosphorylation of glucose in the mitochondria. Tissue inflammation (via the Haber-Weiss reaction) leads to free ion converting superoxide into highly toxic hydroxyl free radical.

Antioxidants convert free radicals back to healthy molecules again. Antioxidants such as vitamin C have been shown to be major combatants to fight disease ever since the 1950's when Harman discovered the role of free radicals (Harman, 1956). The rationale for vitamin C infusion in CFS/ME rests on the use of megadose vitamin C infusion treatments traditionally in autoimmune disease, allergy and a range of other conditions (Kodama *et al.*, 1996).

Multiple chemical sensitivity, together with raised nitric oxide, plus an increase in blood-brain barrier permeability and gut wall permeability will lead to a group of patients with an inability to prevent toxic overload within the neuraxis. Furthermore they lead to an inability to cope with the toxins.

The results of recent research confirm that the immune system is activated in CFS/ME and may offer a future pathological differential diagnostic test between CFS/ME and depression. In a controlled study examining peripheral blood mononuclear cells, concentrations of beta-endorphin, an endogenous opioid involved in regulation of the immune system function, were found to be significantly lower in patients with chronic fatigue syndrome than in normal subjects and depressed patients ($p < 0.001$ and $p < 0.01$, respectively). Also they were significantly higher in depressed patients than in controls ($p < 0.01$) (Panerai *et al.*, 2002).

## 1.5.9 Other treatment protocols

Numerous treatment strategies have been suggested for CFS/ME over the last few decades with most involving some pharmacological intervention. Yet it is interesting that the majority of successful trials have been non-drug based, namely graded exercise therapy

(Fulcher and White, 1997 and 2000), pacing (Hutchinson *et al.*, 2002), cognitive behavioural therapy (CBT) (Deale *et al.*, 1996) and osteopathic treatment (Perrin *et al.*, 1998). Graded exercise has been shown to improve the patient's performance when substituting activities that exacerbated stress levels with more relaxed, mood enhancing activities (Friedberg, 2002). A recent trial demonstrated good outcomes after 1 year for patients with CFS/ME who received an educational intervention designed to encourage graded activity. Benefits of the intervention were maintained at 2 years. Delayed treatment is associated with reduced efficacy and requires more intensive therapy (Powell *et al.*, 2004). As with graded exercise, pacing and CBT techniques probably help improve the symptoms in that they reduce the physical or psychological stress on the body's sympathetic nervous system

### 1.5.9.1 Graded activity

Many in the psychological "camp" believe that patients with CFS/ME perceive greater fatigue during exercise as a result of the interaction of psychological distress, physical de-conditioning and/ or sleep disturbance. Most psychiatrists believe that the patient's fear of worsening their symptoms may lead to reducing their activity and that the resultant physical deconditioning can spiral into chronic disability which further leads to adverse psychological effects. The rationale of graded activity is to circumvent total inactivity and counter this fear-avoidance and de-conditioning by the introduction of a gentle increase in activity to pre-morbid levels. The patients are expected to follow the prescribed exercises irrespective of any worsening in the symptoms and to combat this "perceived" fatigue and recovery from exertion which differs from patient to patient (Paul *et al.*, 1999).

The idea of graded exercise seems unsuitable, if not abhorrent, to some patients who are struggling just to achieve basic activity at work or home. There is a ceiling, above which activity is counterproductive in many cases (Shepherd, 1998). Friedberg and Jason (2001) advise exercise on an individual patient-by patient basis whilst many clinicians do not recommend it (Shepherd, 1998). However, significant improvement in functional capacity was noted in a year long study involving a graded exercise regime. Unfortunately, nearly

half of the patients studied were taking antidepressants throughout the trial which questions the validity of this study (Fulcher and White, 1997).

### 1.5.9.2 Cognitive behavioural therapy

The effectiveness of Cognitive Behavioural Therapy (CBT) in the treatment of CFS/ME has been comprehensively reviewed. It has been shown to be more effective when delivered by properly trained clinicians in specialised clinics (Reid *et al.*, 2000). Distorted thought patterns may lead to anxiety and depression. CBT is based on the supposition that psychological factors are maintaining CFS/ME in all patients (Blenkiron *et al.*, 1999). Such factors may include faulty beliefs, ineffective coping behaviour or negative mood states (Sharpe, 1996). It is the author's belief that the depression and anxiety are secondary to CFS/ME. This creates a sense of frustration in the patient who also feels a terrible burden on family and friends. This may be exacerbated by reactions of people including health care providers who refuse to acknowledge the existence of CFS/ME. CBT may help the patient with these secondary feelings of guilt and worthlessness.

In a randomised study fulfilling the Oxford criteria, patients receiving CBT were functionally improved, but many reported continuing fatigue (Sharpe *et al.*, 1996). However, in a separate study, patients in the CBT group demonstrated significant improvements in physical functioning and substantial reductions in fatigue (Deale *et al.*, 2000). Some patients in the latter study had a current psychiatric diagnosis and others were receiving additional antidepressant therapy. In most of the British studies into the efficacy of CBT and graded exercise, the inclusion criteria require that patients fulfil the Oxford criteria for CFS/ME. It has been suggested that the Oxford criteria and the original CDC criteria may select patients with two distinct clinical entities and in many trials using the Oxford, also known as the UK criteria, the patients studied may in fact have had a high frequency of psychiatric co-morbidity (Baschetti, 1998).

It is most probable that CFS/ME patients who have difficulty in coping with their illness will benefit from CBT. Like other chronic illnesses, positive coping strategies and lifestyle management approaches may be of significant benefit to the depression and anxiety levels

although there is little evidence that CBT has a significant effect on other symptoms of the illness. It is interesting that when the research patients were diagnosed using the Australian criteria, which excludes psychiatric diagnosis, few differences were noted between the CBT treatment group and the controls (Lloyd *et al.*, 1993).

Avoiding exercise due to a belief that it will exacerbate symptoms has been held responsible for maintaining symptoms in CFS/ME patients (Silver *et al.*, 2002). However, this thesis will show that there is a significant improvement when patients are advised to avoid too much activity and only carry out 50% of their perceived capabilities.

Psychiatrists in one study acknowledged that the lack of illness legitimization ranked high as a source of dissatisfaction for CFS/ME patients, and they suggested it may aggravate the psychiatric condition. In the same study they agreed that the symptoms improved if CFS/ME patients stayed within what they felt to be their physical limits. The psychiatrists felt that the improvement was not due to a reduction in physical strain. They believed the progress was due to the patient's "psychosis" being improved by sense of control over their symptoms (Lehman *et al.*, 2002). This is despite a recent study into sets of twins one with chronic fatigue compared to their unaffected co-twin, which showed that levels of fatigue affect physical functioning (Herell *et al.*, 2002).

### 1.5.9.3 Hypnosis

Hypnosis has been tested in a pilot study involving 3 patients with CFS. Patients reported that hypnosis helped in muscle pain management both at rest and after exertion with a slight improvement in quality of life, but there was no increase in cognitive ability (Gregg, 1997).

### 1.5.9.4 Osteopathy

Another recent treatment pioneered by the author has involved a bio-mechanical procedure. This was originally based on the observation of a high incidence of thoracic spinal dysfunction in the CFS/ME patients presenting at the author's practice between 1989 and 1991, all sharing similar structural dysfunctions. Six such cases are described below.

**Case 1**

Sex: Female

Age: 41

Occupation: Housewife, ex-typist

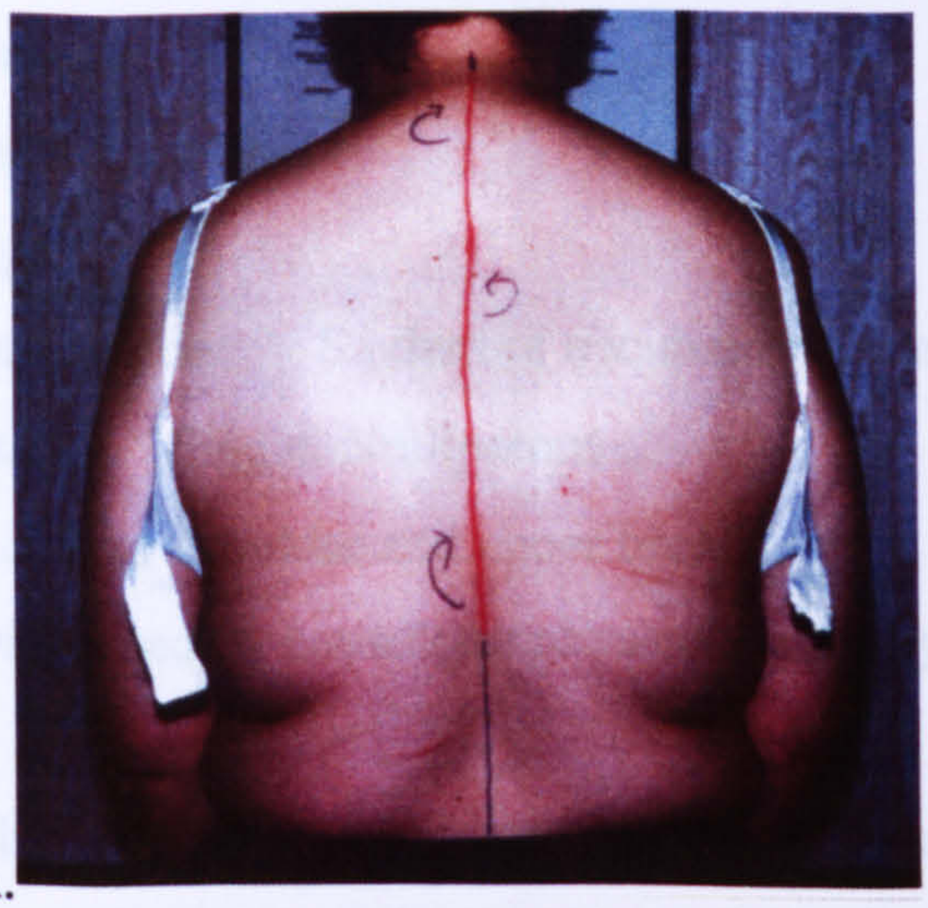
Status: Married, Multiparous

Diagnosed by GP

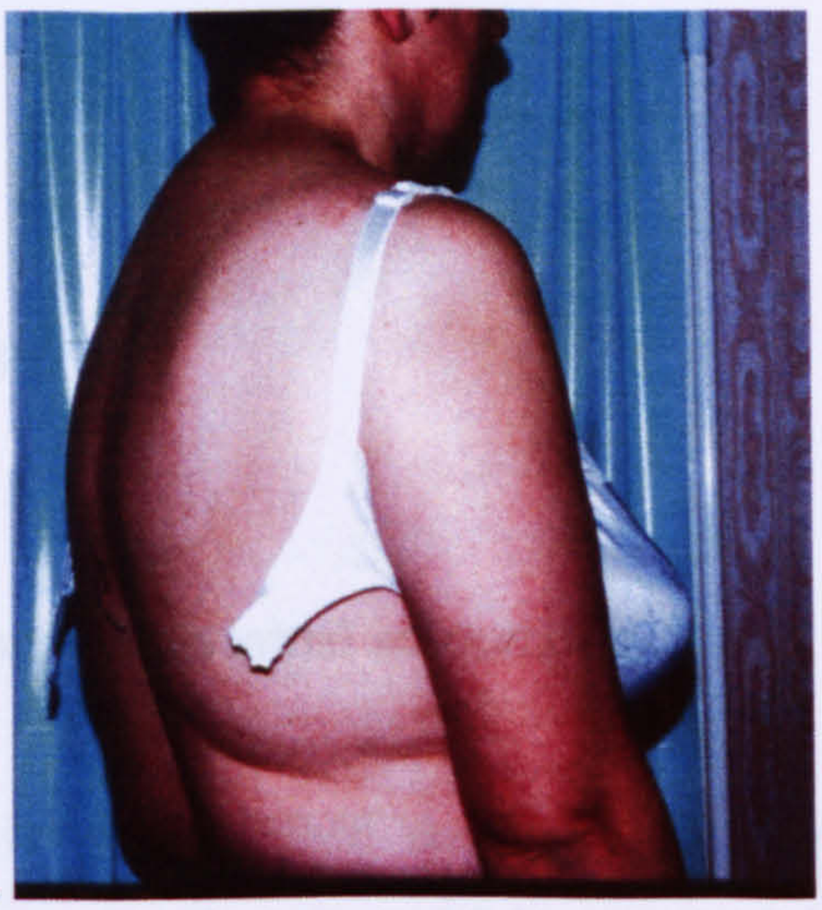
CFS/ME Symptoms began after moving house in the previous year.

Prior aches in low back for a few years.

On examination her dorsal spine presented with a rotational torsion with flatness in the upper part of her dorsal spine, and accentuated kyphosis at the cervico-dorsal junction (Fig. 1A and B).



A.



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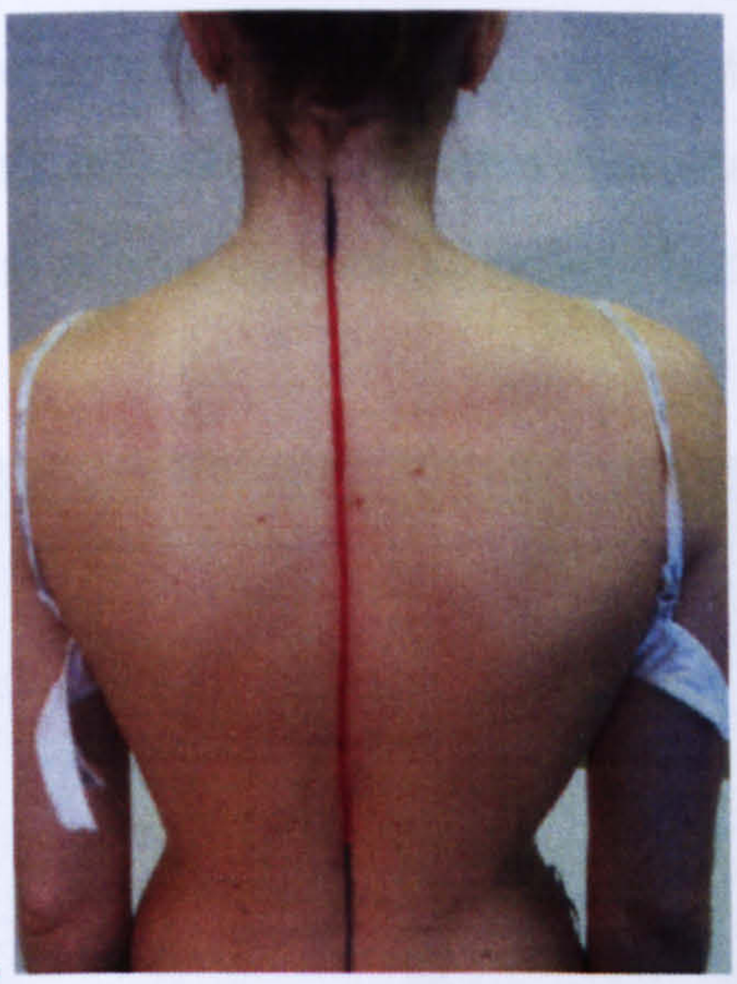

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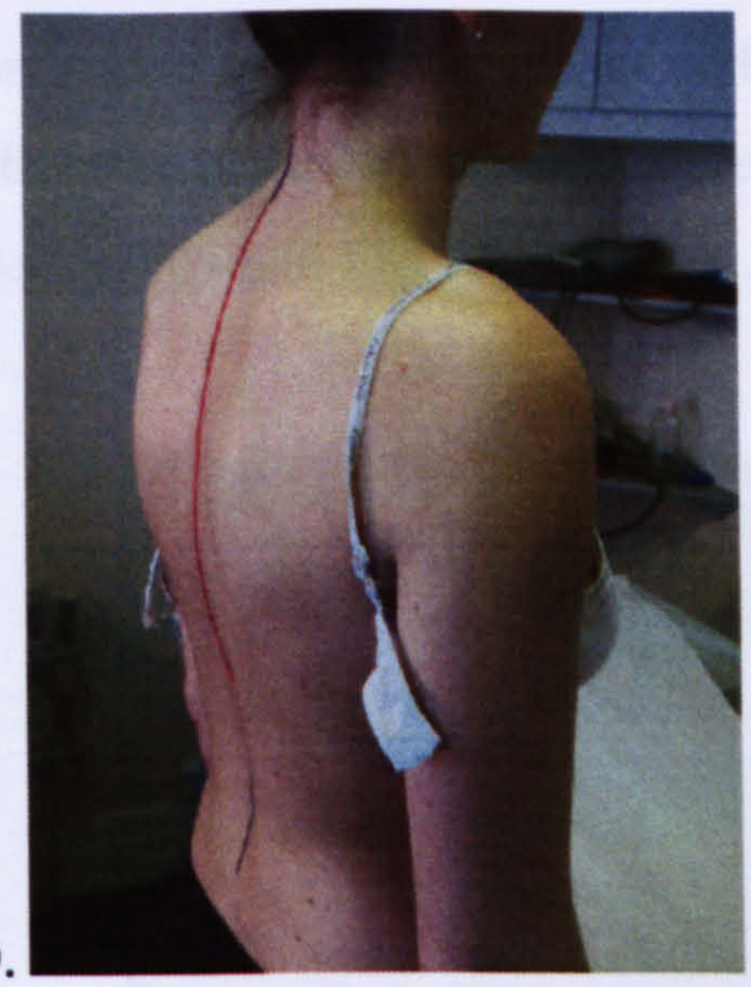


D.

**Figure 1 Case 1 demonstrating rotation and flatness of mid thoracic spine**

Photo A. shows the rotational torsion occurring in a CFS patient's dorsal spine. Photo B. shows flatness in the upper part of her dorsal spine, and accentuated kyphosis at the cervico-dorsal junction. The postural problems in the patient are compared with the normal curvature of a healthy subject seen in photos C and D.

**Case 2.**

Sex: Female

Age: 21

Occupation: Student of occupational therapy.

Status: Single, Nulliparous

Aches in shoulder and upper back.

Diagnosed by consultant physician in one year prior to initial consultation.

This student was not too severely affected by the CFS/ME and was still able to attend college. There were no severe curves in this patient's spine which may explain partially why her symptoms were not intense. On examination a minor scoliosis was detected in the patient's thoracic spine with a characteristic flatness in the mid-thoracic of her spine rather than the normal convex curve we would expect as shown in Fig. 2A.

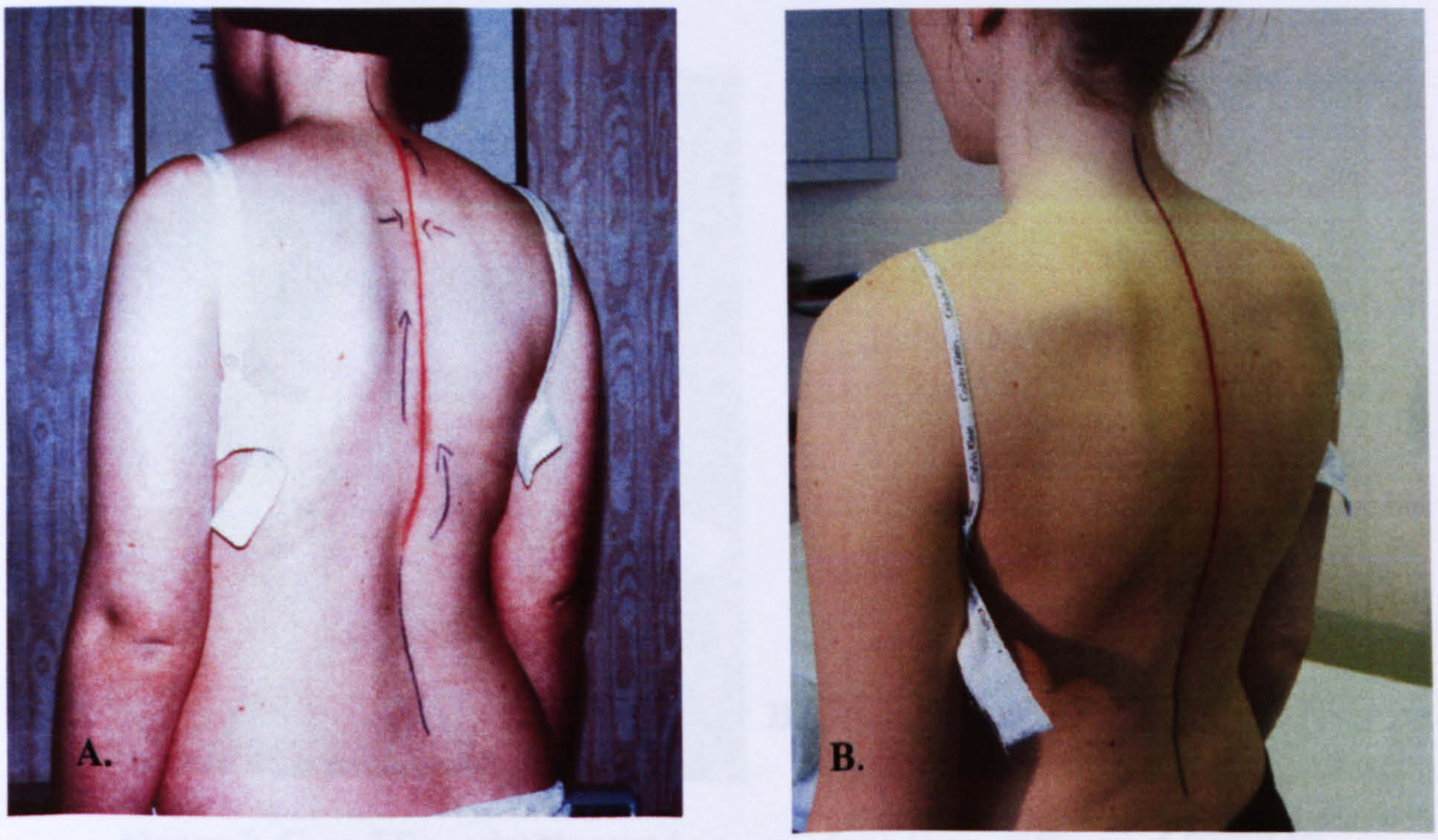



**Figure 2 Case 2 further illustrating flatness and rotation of mid dorsals**

Photo A. demonstrates minor scoliosis in the patient's thoracic spine. The two arrows pointing towards the spinal column show a lordotic region of her spine rather than the normal convex curve we would expect to find at this region. The postural disturbances seen are compared to a normal posture in a healthy subject seen in photo B.

**Case 3**

Sex: Female

Age: 70

Occupation: Housewife, Multiparous

Status: Married

Diagnosed by GP

Suffered for many years with severe pain throughout her body, particularly her back, head and neck. She also suffered with dryness in her eyes and mouth due to a problem with tear and saliva production. This may be due to the disturbance of the sympathetic control of the tear and salivary glands. This patient suffers with degeneration of her spine partly due to her age. There is a kypho-scoliosis in the mid and upper parts of the dorsal spine, where the vertebrae are fused and there is no joint movement whatsoever (see Fig. 3A).

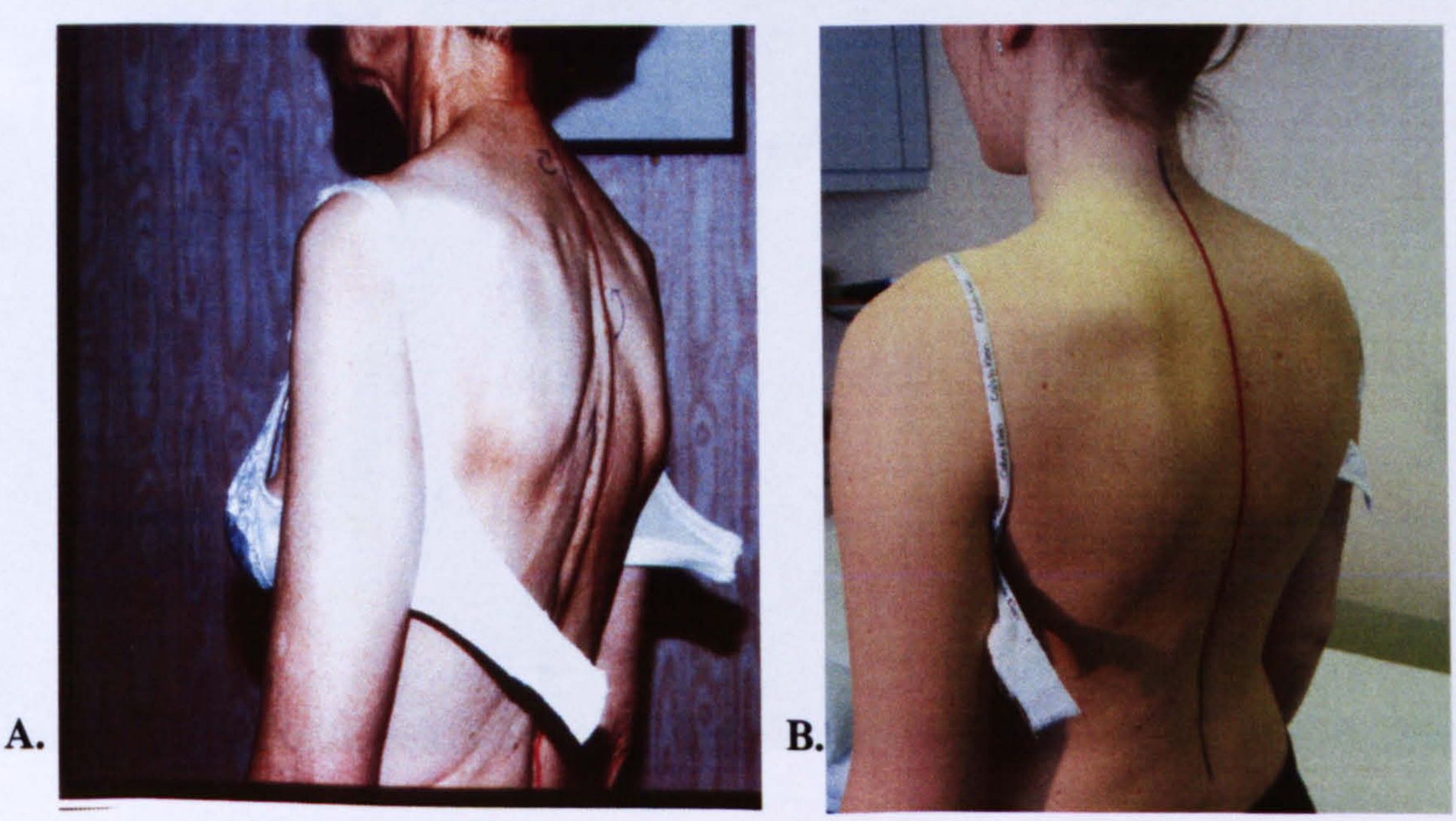



**Figure 3 Case 3 Spondylitis seen in severe long term sufferer of CFS/ME**

Photo A. shows the fusion that has taken place in the patient's thoracic spine due to marked spondylotic changes that have taken place concurrently with over two decades of severe symptoms of CFS/ME. The postural disturbances contrast greatly from a normal s-shaped curvature in a healthy spine seen in photo B.

**Case 4.**

Sex: Female

Age: 24

Occupation: Occupational therapist

Status: Single, Nulliparous

Road Traffic Accident in May 1992, CFS/ME Symptoms began in July 1992.

Diagnosed by her GP.

On examination there was the familiar flattening of the mid thoracic spine. A slight scoliosis of the whole thoracic spine was also noted with a concavity on the left (see Fig. 4A).

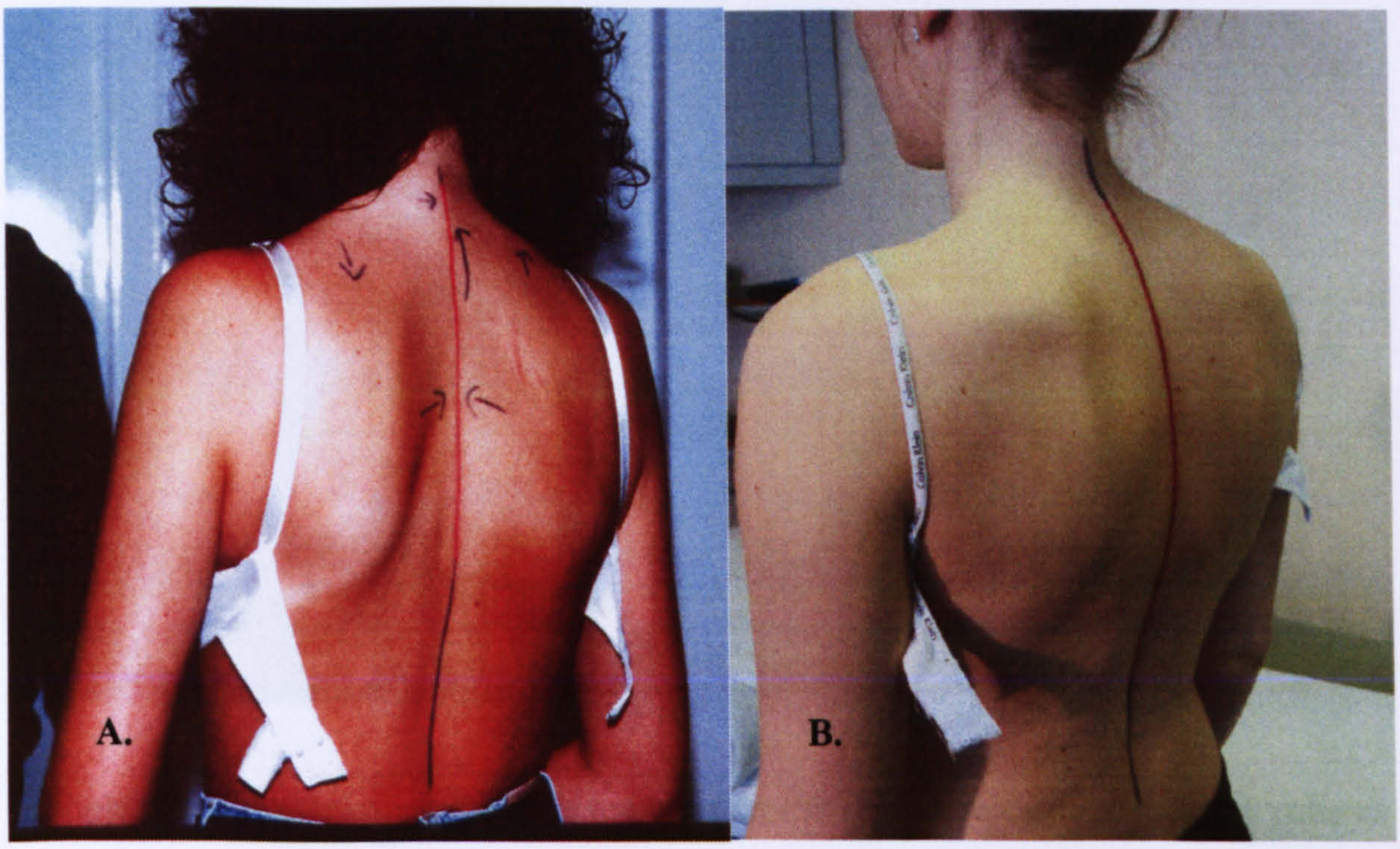



**Figure 4 Case 4 showing a flattened mid thoracic spine**

Photo A. on the left shows the familiar flattening of the mid thoracic spine seen in many CFS/ME patients. This differs from a normal spinal posture in the healthy subject on the right.

**Case 5.**

Sex: Male

Age: 36

Occupation: Shop Manager

Status: Married with young family.

Diagnosed by GP.

Throughout his treatment he managed to stay at work and run his business. As the photograph Fig. 5A indicates, there are no severe curves in this patient's spine, which may explain partially why his symptoms were not intense. The arrows yet again demonstrate a recognisable flatness in the thoracic spine.

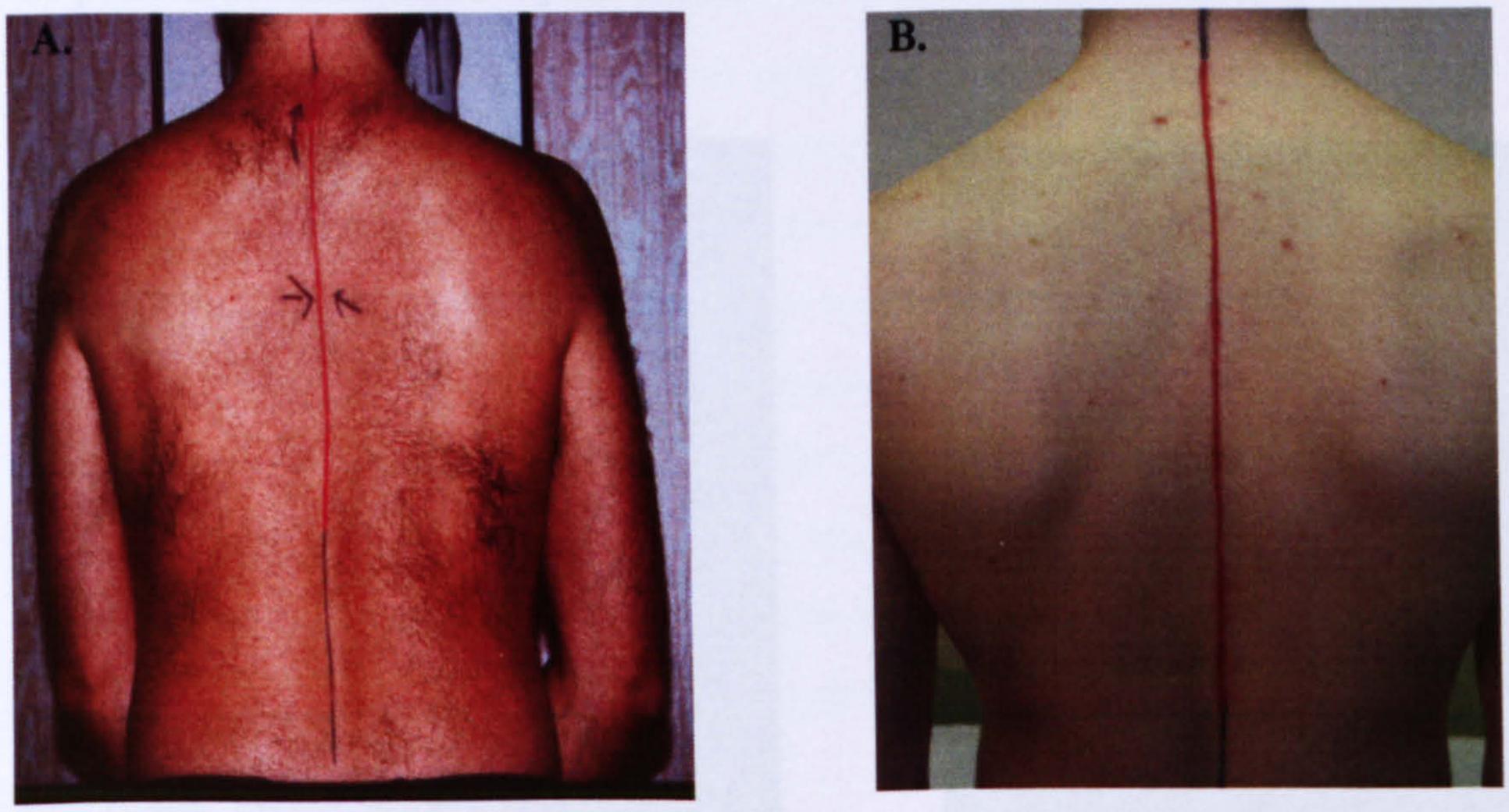



**Figure 5 Photograph showing a male patient with a loss of mid thoracic kyphosis**

In photo A. on the left arrows indicate a flatness in the mid thoracic spine compared with photo B. of a straight and healthy spine

**Case 6**

Sex: Female

Age: 30

Occupation: Credit Controller, clerical work.

Status: Single, Nulliparous

Onset of back pain 1986.

CFS/ME symptoms began seven years later, nine years previous to initial consultation.

Diagnosed By Consultant

On examination the patient presented with a noticeable side bending of the thoracic spine to the right with apparent rotation to the left (Fig. 6A). As with other CFS/ME patients seen by the author, the intense chronic symptoms of this lady seemed to mirror the severity of the postural and mechanical dysfunction.

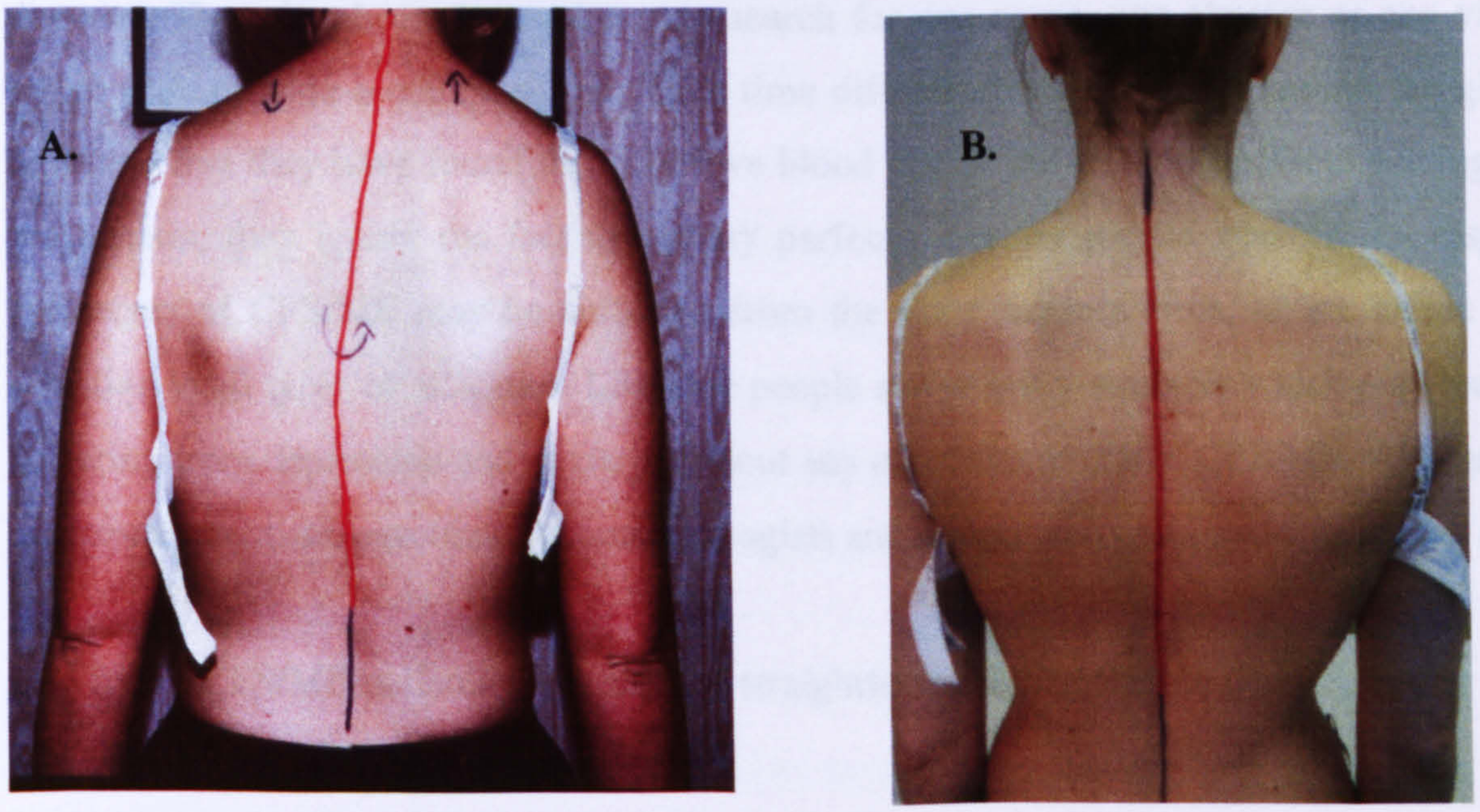



**Figure 6 Case 6 illustrating scoliotic thoracic spine**

Photo A. shows a CFS/ME patient with noticeable side bending of the thoracic spine to the right with apparent rotation to the left. The scoliosis contrasts with the straight healthy spine in photo B.

The above cases are just six of the hundreds of CFS/ME patients examined and treated by the author over the last fifteen years. A sample of thirty nine of these patients, from the author's first three years treating this disorder, are reviewed by the author in section 2.1 to summarise common biomechanical findings. The emphasis on biomechanical dysfunction in CFS/ME is central to this thesis and is reviewed thoroughly in the following chapters.

Many patients suffering from a range of disorders may develop one or more of the symptoms reviewed in the previous sections, yet not develop CFS/ME. In addition, many of the above treatment methods have focussed on single therapeutic approaches, although it would seem logical that no mode, in isolation, would be completely beneficial in an illness that has multiple symptoms involving many body systems (Gantz and Holmes, 1989).

From the review of the literature summarised in this chapter, a major problem exists with the treatment strategies and arguments over the exact aetiology of this most complex disorder. There has been the tendency to search for one cause, one stressor or one virus, which may provide a common link. Each time different research teams around the globe conclude that they have found the definitive blood test or the common pathophysiological mechanism, they ignore the fact that many perfectly healthy people who do not display symptoms of CFS/ME may be suffering from the same suspect virus, or are atopic and sensitive to all types of allergens. Likewise people suffer many stressors which may lead to suffering from depression and anxiety without any other symptoms of CFS/ME. Alternative questions scientists, psychiatrists, immunologists and endocrinologists could be asking are:

a. Why do CFS/ME patients not just have straightforward diagnosable diseases rather than a complex array of signs and symptoms?

b. Is there a common factor that could be affecting all sufferers?

Some authors have chosen to subdivide patients into different groups and claim that there are many diverse types of CFS/ME. There are other scientists who have reached a compromise in classifying CFS/ME. They have recognised that the disease can be viewed

as a complex of psychological, neurological and immunological dysfunction. Glaser and Kiecolt-Glaser (1998) proposed that CFS/ME is a psycho-neuroimmunological disorder with a number of stressors affecting communication between the nervous system, the endocrine system and the immune system.

## 1.6 Aims of the study

This thesis examines certain physiological and anatomical parameters which to date do not appear to have been identified as having a potentially important role in the development of CFS/ME. The primary aims of the study are to investigate the theory that this disease may be associated with a biomechanical disorder affecting principally the lymphatic drainage of the neuraxis via the cerebrospinal fluid (CSF), and to also demonstrate the benefit of a chosen method of osteopathic treatment in reducing the main symptoms associated with CFS/ME.

### 1.6.1 Research objectives

The objectives of this research are:

1 To determine the strength of correlation between the mechanical dysfunction of the spine, and the incidence of the symptoms arising from CFS/ME.

2 To test if a chosen method of osteopathic treatment reduces symptoms associated with CFS/ME compared with those of a matched control group, who receives no such treatment.

3 To reveal the sustainability of any improvement by a year follow up study and to investigate the likely repeatability of the initial study thus strengthening the argument of a relationship between the set osteopathic procedure and the improvement in symptoms associated with CFS/ME.

4 To determine if there is any pathology in the brain that may be causing the symptoms of CFS/ME.

5 To determine if there is any intrinsic muscle disorder that may be causing the symptom of fatigue in CFS/ME.

## 1.6.2 Null hypotheses

The null hypotheses for the objectives listed above are:

1. There is no relationship between the mechanical dysfunction of the spine, and the incidence of the symptoms arising from CFS/ME.

2. There is no difference in the symptoms associated with CFS/ME following a chosen method of osteopathic treatment compared with those of a matched control group, who received no such treatment.

3. Any improvement of symptoms associated with CFS/ME following a chosen method of osteopathic treatment compared with those of a matched control group, who received no such treatment will not be sustainable or repeatable.

4. There is no relationship between pathological findings in the structure of the brain and the symptoms in CFS/ME.

5. There is no relationship between the symptom of muscular fatigue in CFS/ME and any intrinsic disorder of the muscle.

# Chapter 2

# 2 Assessment of the chosen osteopathic method for treatment of CFS/ME: Phase 1: Symptoms, muscle fatigue and spinal mobility

## 2.1 Introduction

The chosen osteopathic method in treating CFS/ME was initially proposed by the author in a clinical review (Perrin, 1994). Initially, the basis for this particular approach was that CFS/ME had a likely origin in dysfunction of the sympathetic nervous system in the thoracic region of the spine.

The concept of CFS/ME being a bio-mechanical disorder requires a substantial paradigm shift in current thinking within the orthodox medical world. Unfortunately before the author's initial research there had been no prior data correlated to demonstrate a connection between the spinal mechanics and the incidence of CFS/ME. With only anecdotal evidence and clinical findings to go on, a review took place at the author's practice of cases seen between 1989 and 1992, where the patients had either presented with CFS/ME type symptoms or had been already diagnosed as suffering from the disorder. Below are two tables summarising the relevant details of thirty nine such patients from this period. None of these patients were included in either clinical trials of phase 1 and 2.

| | | Female Patients | | | |
|---|---|---|---|---|---|
| | | | | | |
| **Age** | **Occupation** | **Area of Dysfunction in Thoracic Spine** | **Acute onset of Back Symptoms** | **Chronic Irritation of Thoracic Spine** | **Time between Onset of Back Problems and CFS Symptoms** |
| 35 | Nurse | All | 4 years | 3 years | 3 years |
| 74 | Housewife | All | N/A | 28 years | 28 years |
| 17 | Student | Upper and Lower | 14 months | 14 months | 3 months |
| 49 | Clerk | All | 30 years | 30 years | 4 years |
| 21 | Student | Upper | N/A | 6 years | 5.5 years |
| 20 | T-sales | Upper | N/A | 10 years | 9.5 years |
| 31 | VDU's | Lower | N/A | 13 years | 4 years |
| 51 | Housewife | Upper + Mid | N/A | 13 years | 9 years |
| 40 | Bookkeeper | Upper | N/A | 4.2 years | 4 years |
| 40 | Teacher | All | N/A | 14 years | 7 years |
| 60 | Clerk | All | 15 years | 15 years | 7 years |
| 29 | Social Worker | Upper | N/A | 4.5 years | 4 years |
| 45 | Teacher | All | 21 years | 21 years | 20 years |
| 32 | Shopkeeper | All | N/A | 7 years | 2 years |
| 48 | Housewife | Upper | N/A | 7 years | 3 years |
| 48 | Teacher | Upper | N/A | 10 years | 4 years |
| 52 | Ex-Teacher | Upper | N/A | 10 years | 5 years |
| 28 | Secretary | Upper | N/A | 10 years | 6 years |
| 22 | Housewife | Upper + Mid | 15 years | 15 years | 11 years |
| 35 | Housewife | Mid | N/A | 10 years | 9.5 years |

**Table 1 Thoracic dysfunction in CFS/ME patients - female**

A table of 20 female patients seen in the clinic of the author between 1989 and 1992 all suffering with thoracic spinal problems together with symptoms associated with CFS/ME. (NB. None of these patients were included in the clinical trials of phase 1 and 2).
N/A = Not applicable as the onset was not acute.
3rd column: all = T1 to T12; upper = T1 to T3; mid = T4 to T7; lower = T8 to T12

| | | Male Patients | | | |
|---|---|---|---|---|---|
| Age | Occupation | Area of Dysfunction in Thoracic Spine | Acute onset Of Back Symptoms | Chronic Irritation Of Thoracic Spine | Time between Onset of Back Problems and CFS Symptoms |
| 46 | Teacher | All | 6 years | 6 years | 0 |
| 46 | Optician | All | N/A | 10 years | 8 years |
| 38 | Dentist | Upper | 9 years | 9 years | 8.8 years |
| 25 | Student | Upper | N/A | 2 years | 1.5 years |
| 30 | Designer | Upper + Mid | 8 years | 8 years | 4 years |
| 36 | Shopkeeper | Upper + Mid | 9 years | 9 years | 5 years |
| 16 | Student | Upper | N/A | 4 years | 3 years |
| 35 | Shopkeeper | Upper | N/A | 5 years | 4 years |
| 27 | Footballer | Upper | N/A | 5 years | 1 year |
| 31 | Ex-Cyclist | All | N/A | 8 years | 1 year |
| 42 | Teacher | All | 20 years | 20 years | 17 years |
| 35 | Student | All | N/A | 12.3 years | 4 months |
| 20 | Student | Lower | N/A | 3 years | 1.5 years |
| 45 | Joiner | Upper | 5 years | 5 years | 3 years |
| 31 | Manager | Upper + Mid | N/A | 16 years | 11 years |
| 26 | Bank Clerk | Upper + Mid | N/A | 12 years | 1 month |
| 29 | Scientist | Upper | 7 years | 7 years | 1 year |
| 60 | Film Director | Upper | N/A | 20 years | 19.5 years |
| 40 | Teacher | Upper | N/A | 1.5 years | 1 year |

**Table 2 Thoracic dysfunction in CFS/ME patients – male**

A table of 19 male patients seen in the clinic of the author between 1989 and 1992 all suffering with thoracic spinal problems together with symptoms associated with CFS/ME. (NB. None of these patients were included in the clinical trials of phase 1 and 2).
N/A = Not applicable as the onset was not acute.
3rd column: all = T1 to T12; upper = T1 to T3; mid = T4 to T7; lower = T8 to T12

The files were selected from patients over the three year period. The first column demonstrates that CFS can strike people from a wide spread of ages. Column 2 shows the variety of different occupations of the patients. The majority were engaged in vocations which place extra strain on the thoracic spine, with the person constantly exerting repetitive

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

The data in tables 1 and 2 indicates which patients suffered from a previous acute injury that might have 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 previous to the onset of CFS/ME symptoms 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 N/A has been placed in this column. Column 5 lists the total time that the patient has been suffering with the spinal symptoms, including stiffness, pain or spondylitis.

The final column shows the length of the interval between the onset of back problems and the commencement of CFS/ME symptoms. This value allowed the relationship between the interval and the nature of the aetiology to be examined.

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

The most prevalent occupations in the CFS/ME patients studied, were Teachers (7 patients), Secretarial/clerical (6 patients), and Students (6 patients). These occupations, in particular are likely to place a major postural strain on the upper spine due to the position adopted at work including spending many hours each day bent over a desk, sat at a computer all day, slumped in an uncomfortable chair in a lecture hall or slouching in an unhealthy easy chair whilst revising. Of the total 39 patients reviewed, 27 (i.e., 69%) were involved in jobs that put extra demand on the thoracic spine, more than any other region of the back.

The average time-lag between the onset of back pain and the onset of CFS/ME seems to differ slightly, depending on the original cause. If at first there was an acute injury, the average time-lag is 6.5 years. If however the aetiology is postural, or due to a chronic repetitive strain, then the average time-lag is 5.8 years.

### 2.1.1 Aims of phase 1

The above patient data pointed to a possible biomechanical cause of CFS/ME. Thus it was concluded that a mode of treatment to improve the biomechanical situation in the thoracic spine may help alleviate the symptoms. The primary aim of this part of the work was to assess the hypothesis that osteopathic treatment reduces the detrimental effect of the symptoms associated with CFS/ME on the patient.

The objectives of phase 1 of the research were:

1. To determine the strength of correlation between the mechanical dysfunction of the dorsal spine specifically hypomobility, with or without inflammation, lordosis or kyphosis, and the incidence of the symptoms arising from CFS/ME.
2. To demonstrate and evaluate the effectiveness of the osteopathic method developed by the author, in the treatment of CFS/ME, utilising self report questionnaires, clinical examination and objective muscle-fatigue tests.

## 2.2 Patients and methods

The study was a repeated measures and a matched between-group design. The initial year-long study carried out in the department of Orthopaedic Mechanics at Salford University was aimed at evaluating the effect of osteopathic treatment in reducing the main symptoms associated with CFS/ME. In that initial project, which began in July 1994, a study was carried out on the symptoms of forty volunteers who had suffered from CFS/ME but received no other new therapy over the 12 month period of the study, except for the chosen osteopathic treatment. Symptoms were assessed using self report questionnaires and compared to those of forty control group members who were allowed any therapy except the chosen osteopathic treatment during the same 12 month period. Muscle fatigue plus spinal mobility were examined in the patient group.

The patient and control group were all aged between 18 and 55. Both groups were matched for marital status with a value of 1 allocated to a single person and 2 if the subject had a partner. There were 33 patient group members who completed the year with five being disqualified for not fulfilling the inclusion criteria, one had to leave the country,

unexpectedly and one dropped out (see Table 3). 16 control group members failed to comply with the instructions over the year and so only 24 controls completed the study satisfactorily (see Table 4). Both the patient and control groups who completed the study contained slightly more single subjects than married scoring an identical mean of 1.42 with equal standard deviations of 0.5. The two groups who completed the year's project were also matched for gender with 17 women and 7 men in the control group compared with 22 women and 11 men in the patient group. All participants in the study volunteered for twelve months, and met the Centres for Disease Control and Prevention (CDC) revised working case definition for chronic fatigue syndrome (Fukuda et al., 1994). The CDC criteria, originally formulated by Holmes et al. (1988), are the internationally accepted standard criteria required for any valid research project involving subjects diagnosed as suffering from CFS/ME. These criteria have been used in other major research projects on CFS/ME patients in this country (Costa et al., 1994).

The London Criteria was also used in this study to determine the CFS/ME diagnosis of patients. This was formulated by scientific advisors for the ME association and Action for ME, based on criteria (Ramsay, 1978; Dowsett et al., 1990) proposed in the Report of the National Task Force on CFS (Tyrrell et al., 1994). They are more stringent than the CDC criteria and pay particular attention to two factors when diagnosing CFS/ME for research purposes. Many of the symptoms and signs evident in people suffering from CFS/ME could be due to a large number of other important conditions. Furthermore, CFS/ME may be active in parallel with other diseases having similar symptoms and signs.

The study was approved by the Research Ethics Committees of both Salford and Bury Health Authorities (see appendix A1).

### 2.2.1 Inclusion criteria

Initially, a total of eighty patients volunteered to take part in the project. They had either been diagnosed as suffering from CFS/ME by a consultant or their GP. They had also been excluded from having any other major untreated pathology. Forty sufferers had asked to be group members and forty had volunteered to be members of the patient group. They all had

initially responded to a notice in the national CFS/ME journal ' INTERACTION', or had heard about the project through word of mouth. All the subjects selected for the project had to satisfy the following criteria:

1. Subjects were aged between18 and 55 inclusively.

2. Subjects in both the osteopathically treated and control groups had to conform to the Centre for Disease Control diagnostic criteria for Chronic Fatigue Syndrome and the London Criteria for ME.

3. Members of the patient group were able to afford £400 of treatment over the year period at a rate of £20 per treatment for twenty sessions. If further treatment was required during the year, it was given free of charge.

4. The patients receiving osteopathic treatment were able to travel to and from the treatment clinics in Salford, Prestwich or Manchester.

5. Subjects understood the importance of continuing the treatment until the end of the year, although they knew they were free to leave the project at any time.

6. Subjects had to be honest at all times with the author and any members of his research team regarding the amount of exertion placed on the pad when testing for muscular fatigue.

7 The patient was willing to be part of a longer follow-up study.

## 2.2.2 Exclusion criteria

1. Patients receiving other treatment for their CFS/ME symptoms were excluded from being part of the patient group, unless they had received the other treatment as ongoing therapy for at least six months prior to the start of their participation in the project.

2. Patient group members receiving any other manual treatment for their CFS/ME symptoms other than from the author were excluded from the study. Subjects were also

eliminated from the project if they had received any prior physical therapy for their present symptoms.

3. Any group members receiving any form of manual treatment for their CFS/ME symptoms were also excluded from the trials.

Subjects were also excluded from the study if they exhibited any of the following:

4. Premorbid symptoms of depression.

5. If there was a doubt as to the psychiatric state of the patient, or the subject was experiencing a primary depressive illness.

6. Any psychiatric history in the family

7. Tested positive for any other untreated pathophysiological cause of the symptoms.

8. If they had suffered from any other neurological disorder.

9. If there was reasonable doubt as to the compliance of any member of the treated patient group with any of the author's instructions specifically regarding exercises and lifestyle changes.

10. If there was any misgiving concerning the veracity of any individual subject's isometric tests due to pushing with far less effort than reasonably expected.

11. If a subject's questionnaires produced conflicting answers on a regular basis demonstrating a lack of concern, or worse, a deviation from the truth.

| Code No. | Gender | age | Status |
|---|---|---|---|
| RP01 | F | 32 | S |
| RP02 | F | 35 | S |
| RP03 | F | 23 | S |
| RP04 | F | 22 | S |
| RP05 | F | 31 | S |
| RP06 | F | 49 | S |
| RP07 | M | 29 | S |
| RP11 | M | 39 | M |
| RP12 | F | 38 | S |
| RP13 | F | 44 | M |
| RP14 | M | 41 | S |
| RP15 | F | 34 | S |
| RP16 | F | 53 | M |
| RP17 | F | 42 | M |
| RP19 | F | 51 | M |
| RP20 | F | 40 | M |
| RP21 | F | 28 | S |
| RP23 | M | 26 | S |
| RP24 | F | 28 | S |
| RP25 | F | 40 | M |
| RP26 | M | 44 | M |
| RP27 | F | 18 | S |
| RP28 | M | 47 | M |
| RP29 | M | 27 | S |
| RP30 | F | 52 | M |
| RP31 | F | 47 | M |
| RP32 | M | 46 | M |
| RP33 | F | 43 | M |
| RP34 | M | 27 | S |
| RP35 | F | 42 | S |
| RP36 | M | 32 | M |
| RP38 | M | 30 | S |
| RP40 | F | 34 | S |
| | Female=22<br>male =11 | Mean=37 | Single=19<br>married=14 |

**Table 3 Demographic data of patient group members – phase 1.**

This table lists all the CFS/ME patient group members who completed the year-long course of osteopathic treatment during phase 1 of the study. Note in final column, divorcees were classified as single.

| Code No. | Gender | Age | Status |
|---|---|---|---|
| C01 | F | 41 | S |
| C05 | M | 38 | S |
| C08 | M | 39 | S |
| C10 | M | 33 | S |
| C14 | F | 40 | S |
| C17 | M | 36 | S |
| C19 | F | 22 | S |
| C21 | F | 21 | S |
| C22 | F | 36 | S |
| C23 | F | 41 | M |
| C25 | F | 42 | S |
| C26 | F | 45 | M |
| C27 | F | 49 | M |
| C28 | M | 46 | M |
| C30 | F | 54 | M |
| C31 | M | 47 | S |
| C33 | F | 47 | M |
| C34 | F | 49 | S |
| C35 | F | 40 | M |
| C36 | F | 46 | M |
| C37 | M | 45 | M |
| C39 | F | 45 | M |
| C40 | F | 39 | S |
| C41 | F | 34 | M |
| | 17 female | mean =41 | 13 single |
| | 7male | | 11 married |

**Table 4 Demographic data of control group members – phase 1.**

This table lists all the control group members who remained on the study for the entire year of phase 1. The control group consisted of CFS/ME sufferers not having osteopathic treatment. Note in final column, divorcees were classified as single.

## 2.2.3 Symptom assessment

The members of the treated group received code numbers RP01 to RP40 to protect their anonymity. They also received secret code numbers which were given to them by an independent observer to be used by the subjects when completing their questionnaires. The identity of the secret code was kept hidden from the researcher until later on in the project. This number allowed the patient the freedom to answer the questionnaires truthfully

without the researcher influencing the reply given. This system was adopted to reduce bias and thus increase the validity of the questionnaires. The control group members were coded C1 to C41.

Improvement in the condition of each CFS/ME subject, as well as each subject group, was assessed utilising objective and subjective measures of each of the main symptoms of CFS/ME. The measurements were carried out using laboratory tests and self report questionnaires. Background research material was evaluated to validate the use of the questionnaires in this study (Beck *et al.*, 1979; Beck, *et al.*, 1988; Hunt *et al.*, 1981; Broadbent *et al.*, 1982; Tomeny and Morgan, 1900; Behan and Bakheit, 1991; Smith, *et al.*, 1993; Ray *et al.*, 1993; Schmaling *et al.*, 1994; Swanink *et al.*, 1995). Finally, objective investigative procedures, and recognised diagnostic tests for CFS/ME were examined (Fukuda *et al.*, 1994; Costa *et al.*, 1995).

### 2.2.3.1 Questionnaires

The following eight self-report questionnaires were filled out by all members of the patient and control groups every three months for the year. A follow up set of questionnaires were completed by the patient group at one year after the conclusion of the study to see if any improvement that occurred after 12 months of treatment was maintained. It did not prove possible to determine a one year follow up score for subjects of the control group as some of them had opted for manual treatment and several patients did not wish to carry on cooperating with this research. Although it would have been preferable to compare the follow up results with the control group, the main reason for a follow up was to see if any improvement in the patient group was sustained and this could still be evaluated without reference to the control group's progress. Thus only the patient group was assessed in the follow up study.

The first two questionnaires were developed by the author specifically for this study and tested in a pilot study. Questionnaires 3 to 8 were chosen for the project as they had already been sufficiently validated by inclusion in previous research studies, most involving

CFS/ME. After examining other similar inventories and reviewing the literature on these questionnaires, they were deemed suitable, precise, and easy to use (See Appendix A6).

Questionnaire No. 1

HEALTH: General Health questionnaire, which was developed especially for the study and was based on twenty six of the most common symptoms, complained of by CFS/ME patients. This health score increased with the severity of the symptoms. Although many of these symptoms were included in the other questionnaires, it was felt that an extra general health questionnaire would strengthen their validity

Questionnaire No. 2

BACK PAIN: This was developed by the researcher to examine any correlation between the amount of back pain and the severity of the other symptoms associated with CFS/ME.

Questionnaire No. 3

THE REVISED BECK DEPRESSION INVENTORY (Beck et al., 1979): This was chosen as the most suitable questionnaire for assessment of depression. It was short and required only 5 – 10 minutes to complete. It was quick and easy to score and had a cut off point. Over the last 26 years, the BDI has become one of the most widely accepted instruments for detecting and assessing the intensity of depression in non-psychiatric patients (Beck et al., 1985).

Questionnaire No. 4

THE BECK ANXIETY INVENTORY (Beck et al., 1988): The author's previous clinical findings revealed a high level of anxiety in patients diagnosed as suffering from CFS/ME. Given that anxiety and depression frequently co-exist (Clark, 1989; Watson and Kendall, 1989), the results from instruments designed to measure the severity of anxiety or depression had been found to be highly correlated with one another (Beck, et al., 1988; Gotlib and Cane, 1989). The BAI was formulated to measure symptoms of anxiety which are minimally shared with those of depression, and thus it was a suitable anxiety

questionnaire to use with the BDI. It was formulated to use with adult populations. Furthermore, it is simple and quick to fill in and score.

Questionnaire No. 5

THE MORGAN-GLEDHILL SLEEP QUESTIONNAIRE (Tomeny and Morgan, 1990): Sleep disturbance is one of the most common symptoms of CFS/ME (Krupp, 1993). A recent study showed that many patients with CFS/ME had trouble staying asleep (Schaefer, 1995). EEG and actimetering (Horne et al., 1994) measuring techniques were first considered for the project but were found to be too costly and difficult to use. The Morgan-Gledhill sleep questionnaire was one of only a few established sleep questionnaires which provide a score suitable for statistical analysis. The exact scoring system chosen is seen on the questionnaire in Appendix A6.

Questionnaire No. 6

BROADBENT'S COGNITIVE FUNCTION QUESTIONNAIRE (Broadbent et al., 1982): Pronounced and frequent deficits have been found in patients with CFS/ME when attempting to carry out performance tests (Daugherty et al., 1991). Originally the use of practical cognitive function tests was considered. However, these tests can only be satisfactorily assessed when they are carried out on the control group as well as the patient group. Since no direct contact was made with the control group by the author, it was decided to use a cognitive function questionnaire. The Broadbent's CFQ was previously validated through its use in other CFS/ME research projects (Smith et al., 1993).
Again this questionnaire was easy to complete and score.

Questionnaire No. 7

THE NOTTINGHAM HEALTH QUESTIONNAIRE (Hunt et al., 1981): It was felt that the Nottingham Health Questionnaire is a quick, simple indicator for the general symptoms of CFS/ME and widely accepted. Dr. Charles Shepherd, the then medical advisor of "The ME Association", advised the author to include this questionnaire in the project to gain acceptance of the research findings by his national group.

Questionnaire No. 8

THE PROFILE OF FATIGUE RELATED STATES (Ray et al., 1992): The PFRS is a multidimensional measure incorporating nearly all the symptoms associated with CFS/ME. It was developed at Brunel University especially to measure the symptoms of this illness and evaluate the effects of treatments (Ray et al., 1993). It is longer than the other questionnaires, but it is still quite easy to complete and not too difficult to score. It has four scales: emotional stress, cognitive difficulty, fatigue and somatic symptoms.

These eight questionnaires were not being used to diagnose any disorder, but to compare the function and symptoms of subjects before and after treatment. They also provided a means of comparing the overall health of the patient and control groups. Health psychologist Dr. Pat Hartley PhD (Reader in Psychology, University of Salford) was directly involved in the entire running of all the psychological tests. She was licensed to perform all the questionnaires included in this study.

The mean scores of the patients for each of these questionnaires were expressed as a percentage, where 100% represented the most severe symptom. Scores took place over 12 months comparing means of each questionnaire of the two groups. Questionnaire 1 (health) had a minimum value of 26 where each separate complaint scored from a range of 1-4 from symptom-free to maximum severity with a highest total score of 104. The back pain questionnaire scored a minimum of 12, as each region of the back scored '1' if pain free with a maximum score of 48. Likewise, questionnaire No. 8 had a minimum value of 54 based upon the score of 1 for each symptom free section with a maximum total score of 378. All the other inventories scored zero for each symptom free item with a maximum total score of 63 for both questionnaires 3 (depression) and 4 (anxiety). Questionnaire 5 (sleep) scored a maximum total score of 14, questionnaire 6 (cognitive ability) scored a maximum of 100 and the Nottingham health questionnaire (No. 7) scored a maximum 38. The complete scoring system for questionnaires 1 to 8 is detailed in Appendix A6 and is summarised in Table 5 below.

| | No problem | Max problem |
|---|---|---|
| Questionnaire No. 1 HEALTH | 26 | 104 |
| Questionnaire No. 2 BACK PAIN | 12 | 48 |
| Questionnaire No. 3 DEPRESSION | 0 | 63 |
| Questionnaire No. 4 ANXIETY | 0 | 63 |
| Questionnaire No. 5 SLEEP | 0 | 14 |
| Questionnaire No. 6 COGNITION | 0 | 100 |
| Questionnaire No. 7 NOTTINGHAM | 0 | 38 |
| Questionnaire No. 8 PFRS | 54 | 378 |

**Table 5 Self report questionnaire scores**

Each questionnaire had a different scoring system. Most had 0 = no problem for different symptoms. However, questionnaires 1, 2 and 8 all had a minimum score of 1 for the individual questions thus their minimum total score was 26, 12 and 54 respectively. The questionnaires and their scoring systems can be seen in Appendix A6.

### 2.2.3.2 Measurement of exercise induced muscle fatigue.

Since fatigue is the most common clinical symptom of CFS/ME, it was considered essential to assess whether there was a reduction of fatigue following osteopathic intervention. Measurement of the strength of the right knee extensors were chosen because clinical practice with CFS/ME subjects had shown that fatigue was particularly evident in these muscles. The fatigue test involved isometric measurement of the static torque exerted about the knee by the extensor muscles of that joint using a specially designed calibrated chair as shown in Fig. 7 below.

Fatigue may be defined as a progressive impairment of maximal force generating capacity that develops during muscular activity. A muscle is said to fatigue when the point at which a contraction can no longer be maintained, the failure point, has been reached. Onset of

fatigue has been found to occur after only a few seconds of maximal-effort muscle contractions (Lewis and Haller, 1991).

During each measurement the patient was seated with the leg hanging vertically. A lever attached to a torque transducer mounted at the level of the knee joint axis was aligned along the lateral side of the leg with a padded extension that projected across the front of the shin. During each test the lever was clamped in a fixed position. The patient was asked to exert as much force as possible against the padded extension and the resulting trace of torque at the knee was plotted against time on a pen recorder. After 30 secs. the patient was instructed to stop pushing.

The main problem encountered in measuring fatigue of the knee extensors was that of achieving maximal force without causing major damage to the patients' muscles. This difficulty was overcome by carrying out a pre-test in which the patient was initially asked to exert a maximal force for just a few seconds followed by a series of pushes at a third of maximum on the leg pad a number of times and then resting for three minutes before the final test. These preliminary ten contractions served a dual purpose. Firstly they allowed patients to accustom themselves to the machine before applying maximal torque for at least 30 secs., and secondly they provided a safe exercise to induce some preset fatigue of the muscle.

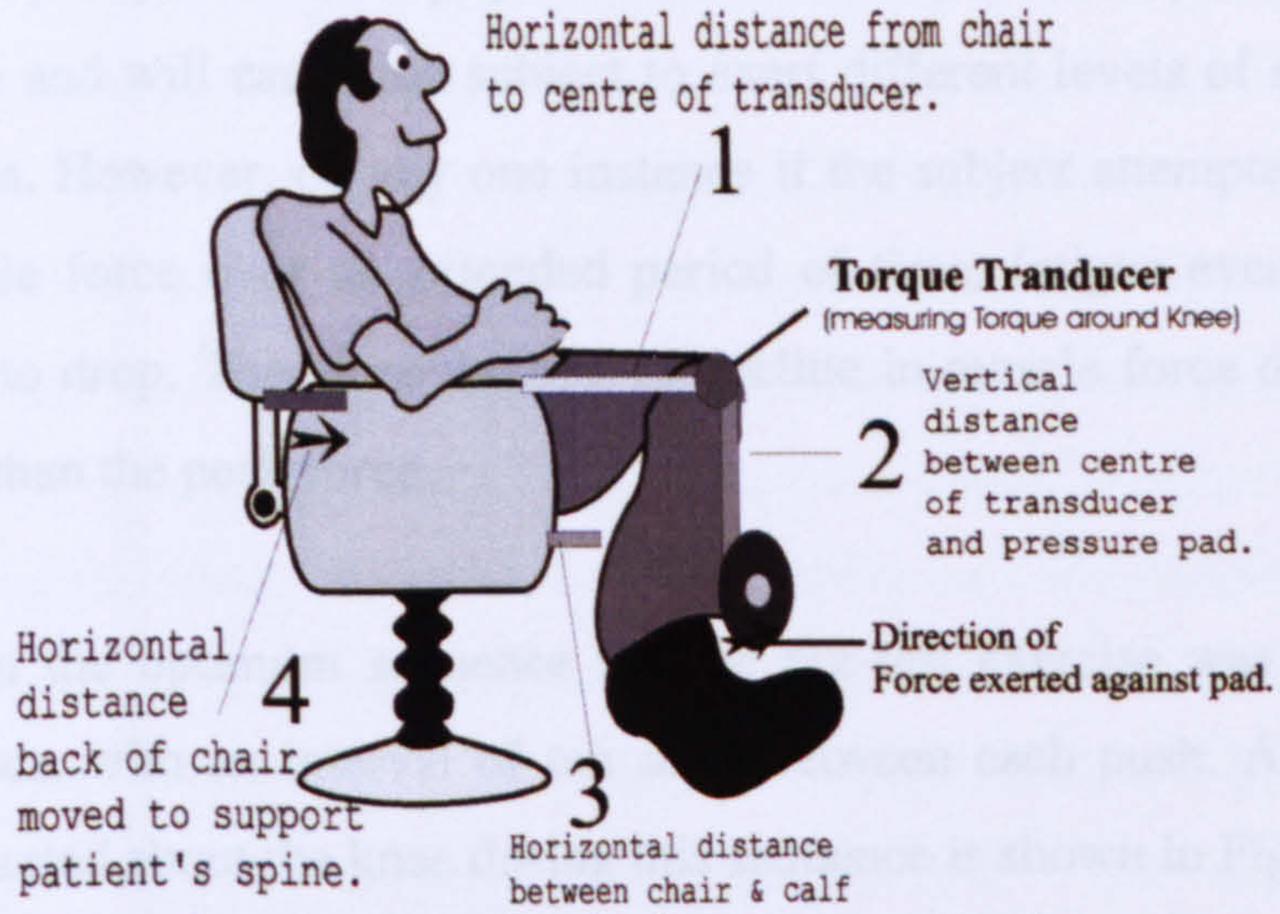



**Diagram illustrating the 4 measurements used to calibrate the chair for each individual patient.**

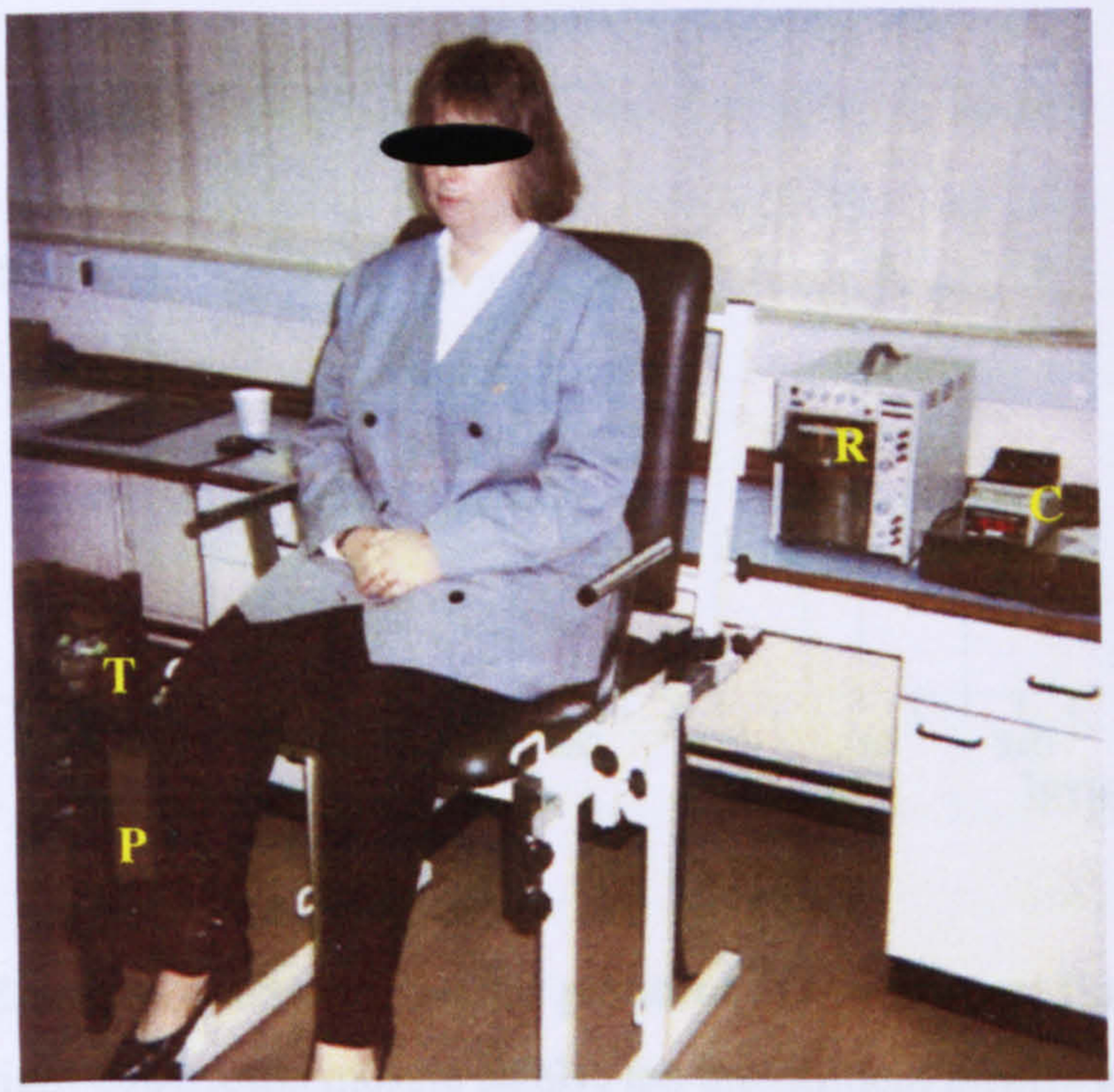



**Figure 7 The Salford biomechanics chair**

T= torque transducer P = pressure pad R = chart recorder C = clock

The top diagram shows the four parameters that were measured before each session in order to ensure that the subject remained in a very similar position as at the start of the study. Below, the photo shows the position of the patient on the chair at Salford University's human performance laboratory.

Everyone has an in-built sensation of discomfort which safeguards them against exerting excessive levels of muscle force which can damage the muscle fibres. This is partly

psychological and partly due to the physical sensation of pain. The psychological element of this is variable and will cause the subject to exert different levels of maximal force on separate occasions. However, on any one instance if the subject attempted to maintain the exertion of muscle force over an extended period of time, fatigue eventually set in and caused the force to drop. Therefore the rate of decline in muscle force due to fatigue was more significant than the peak force.

It was found that the optimum sequence for the pre-test exercise was ten pushes, each lasting twenty secs. with an interval of ten secs. between each push. A typical plot with time of torque exerted about the knee during this sequence is shown in Fig. 8.

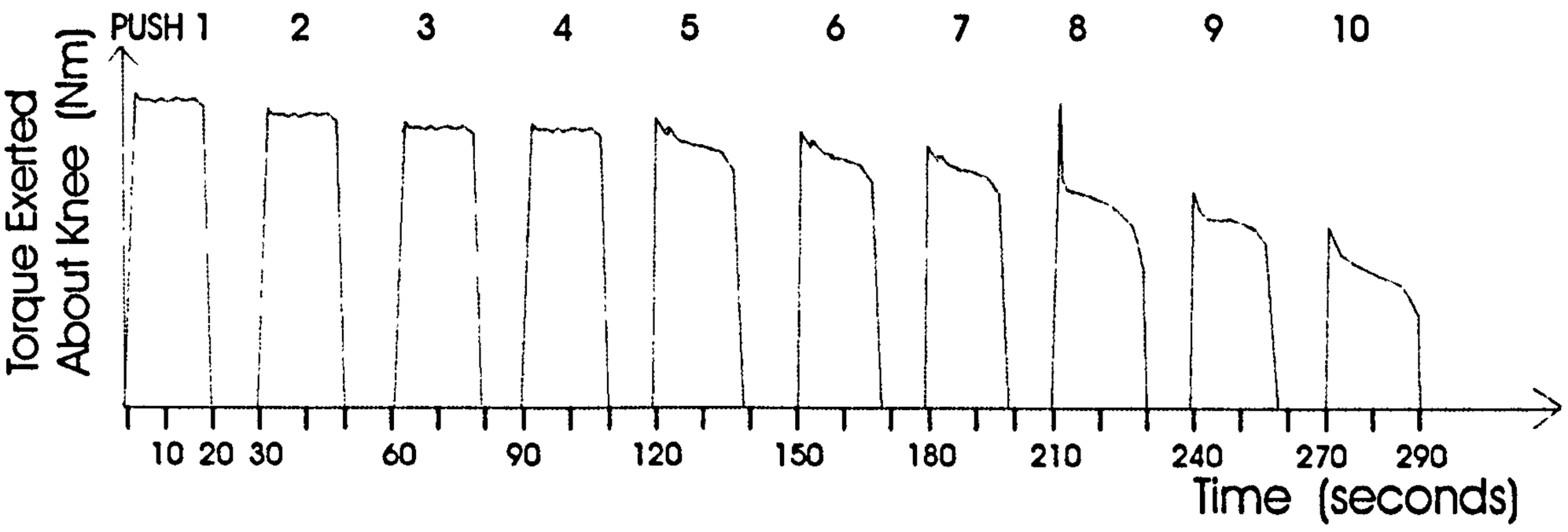



**Figure 8 Example of chart recorder printout of the pre-test fatigue induction**

To fatigue the right quadriceps muscle safely, ten intermittent pushes each of 20 secs. were carried out with an interval of 10 secs. The reduction in the maximum torque and the increase in the graduation of the slope in the latter pushes indicate fatigue in the muscle tested. The patient then rested for three minutes before the final push.

As one can see from the chart above, throughout the first four pushes after the initial peak, the torque was held relatively constant until the subject stopped pushing. During pushes 5, 6 and 7, after the initial peak, fatigue caused a gradual drop in torque over the 20 secs. time period when the patient was attempting to keep the torque at maximum. Sometimes, after a

10 second rest, the subject was able to momentarily achieve an initially high peak torque as in push no. 8 similar to the original level at push no. 1. However, this was short lived and subsequently torque levels rapidly fell to a magnitude below push no 7. By the tenth cycle of pushes the effect of fatigue had become fully established. A similar picture of fatigue with exercise pushes was evident in all of the patients, as well as the normal group selected from university staff for the pilot study. Therefore, ten repeated push cycles was chosen as the *modus operandi* to induce fatigue in all the isometric tests completed in both phases of this study. After completing these ten cycles the subject was allowed three minutes rest for the muscles to recover. Then, the patient was asked to push as hard as possible again, only this time they were requested to maintain the maximal push until they could no longer continue. During early tests a difficulty arose in evaluating exactly what was meant by 'as long as possible'. It was not the author's intention to cause muscle damage and this would have added far too many subjective factors into the experiment increasing the margin of error. In the preliminary pilot test it was noted that CFS/ME patients could sustain a thirty second final push before relaxing. Subsequently the first thirty seconds were chosen to evaluate the muscle fatigability. The patient was then told to stop pushing after this time to prevent any injury. A typical recording for this final push is shown in Fig. 9, where the torque about the knee axis is plotted vertically against time on the horizontal axis.

Newton's second law states "The change in linear momentum of a body under the action of an unbalanced force will be proportional to the product of the force and the time for which it acts" This change is known linearly as impulse. In Fig. 9, where the torque about the knee axis in Newton metres is plotted vertically against time on the horizontal axis, this product of torque x time is represented by the area under the graph. This area, coloured yellow on the graph, is an angular measurement of the change in impulse torque over the first thirty secs. of the final push test. The torque, also known as the turning moment, is defined as:

$M = F \times d.$

Where M=Turning Moment

F = the magnitude of force (how hard the patient pushes)

d = the perpendicular distance of the line of action of the force away from the centre of rotation of the knee joint.

The area under the pen recorder graph of torque against time, the impulse torque, was measured by counting the minute boxes of the recorder readout. It relates to the maximum torque produced and how long it may be sustained. It is inversely proportional to the fatigue of the muscle and thus is a good indicator of the fatiguability of the knee extensors. Hence, the larger the area under the graph, measured in Newton metre seconds (Nms), the less the fatigue of the muscle.

The impulse torque has been mistakenly referred to as work done by the muscle. From a true mechanics viewpoint, this is not valid, although it can be related to the physiological work done in the cells of the muscle to produce energy for the contraction. With isometric exercise no actual movement in the joint takes place. Therefore no biomechanical work has been done, work done being the product of force x distance (Richards, 1999).

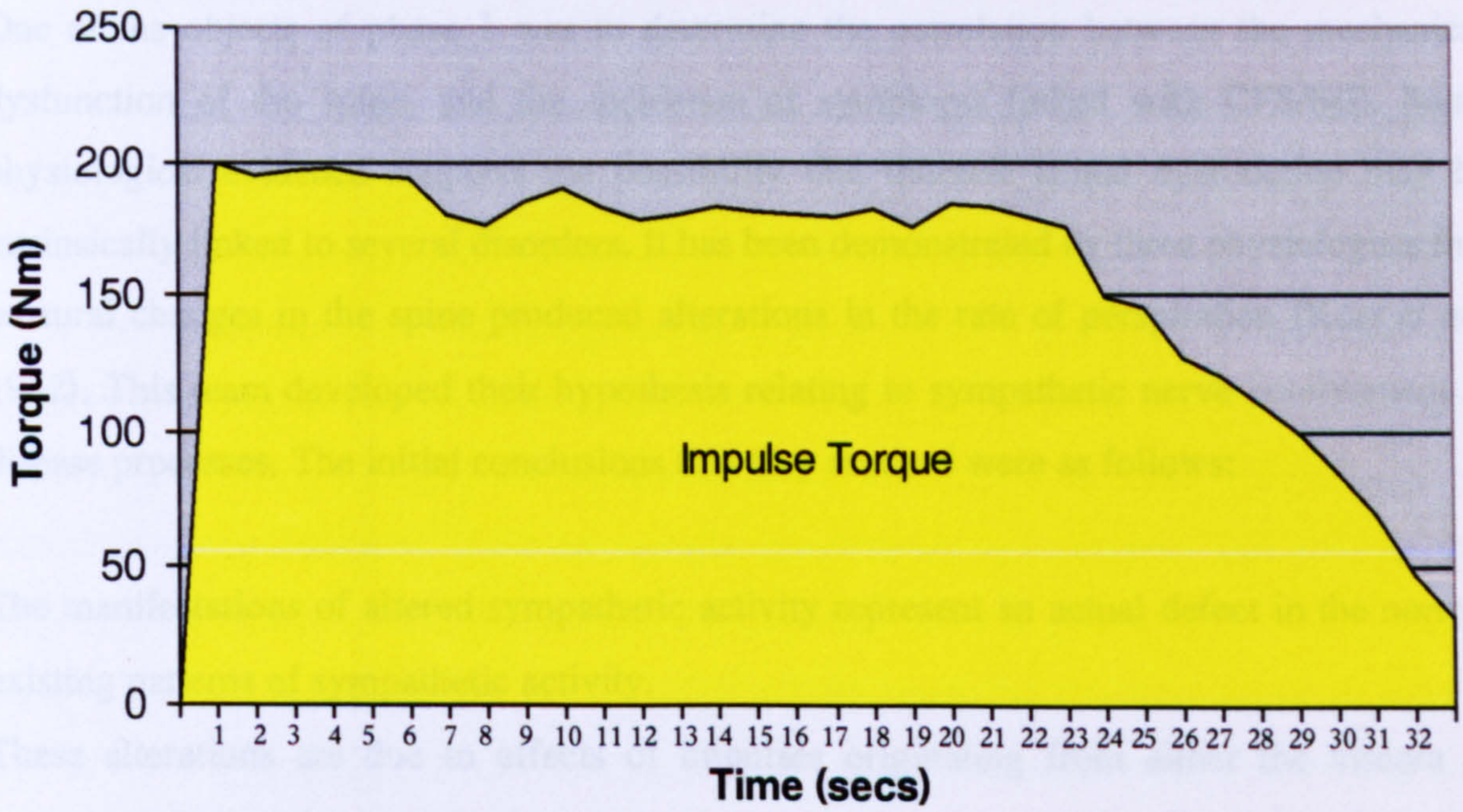



**Figure 9 The measurement of impulse torque**

The graph of time (x-axis)/seconds V Torque (y-axis) / Newton metres of the final push which took place exactly three minutes after the end of the ten pushes shown in Fig. 8. The impulse torque is the area under the graph. This area for the first 30 seconds was measured by count of boxes on pen recorder paper. A reduction in fatigue was indicated if this area increased compared with earlier results.

After each test the subjects' final push were rated on the Borg Scale of Perceived Exertion (Borg and Linderholm, 1970). This perceptual effort rating was formulated as a behavioural and psychological measurement of physical performance and work capacity. The real value of exertion is proportional to the heart rate of the patient i.e. if the pulse after exertion was 100 then the real value of exertion scored 10 on the Borg scale (see Appendix A7).

Each subject was asked to score the perceived amount of strain they felt during the last exercise by using the Borg scale where 6 = minimum effort required and 20 = maximum effort required. As long as the difference between the real and perceived exertion during the initial tests did not increase in the final test, then any torque improvement would imply that the patient was not simply putting in more effort at the end compared to the beginning of the project.

### 2.2.3.3 Thoracic spinal mobility

One of the objects of phase 1 was to determine the correlation between the mechanical dysfunction of the spine, and the incidence of symptoms linked with CFS/ME. Some physiological evidence supports the possibility that thoracic spinal dysfunction may be intrinsically linked to several disorders. It has been demonstrated by three physiologists that postural changes in the spine produced alterations in the rate of perspiration (Korr *et al.*, 1962). This team developed their hypothesis relating to sympathetic nerve involvement in disease processes. The initial conclusions that they reached were as follows:

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

These alterations are due to effects of impulses originating from either the viscera or somatic sources.

Other components, such as adaptive or pathological changes, and altered excitability within the central nervous system, may eventually become involved. This may directly affect local tissues outside the expected route of the nerve impulses.

Further studies revealed that areas of altered sympathetic activity also appeared in apparently normal subjects. Korr (1978) suggested that this was due to sub-clinical bombardment of nerve impulses into the spinal cord. These impulses cause no symptoms themselves but, added to other stimuli affecting the same spinal segment they could combine to cause major problems. Long lasting hyperactivity of innervating sympathetic pathways seems to be a prevailing theme in many clinical conditions, involving various organs and tissues (Korr, 1978).

Korr also suggested that spinal dysfunction would lead to disturbances in the muscular fatigability, sensory excitability, immunological mechanisms and endocrine functions due to impairment in normal sympathetic efferent flow (Korr, 1979). Based on this hypothesis, it was felt that a method to determine spinal mobility was needed in the present study. If the amount of movement in the thoracic spine was shown to be proportional to the symptom picture, then it could support the hypothesis concerning a possible spinal link in a mechanical aetiology of CFS/ME.

There are many methods of measuring mobility of the spine, and several were assessed ranging from the use of a flexicurve (Burton, 1985), to the more technological MAC Reflex, which utilises infra-red scanning together with computerised digitisation. The latter was found to be too time consuming, and difficult to use as it had to be re-calibrated after each patient. The chosen method involved the use of the Salford Biomechanics Work-station. This device digitised the movement of the thoracic spine from video film of the patient bending forwards from an upright position to full flexion. The patient was positioned with the camera placed laterally focused on three probes that were fixed by adhesive tape to specific points on the subjects back overlying the spine when the subject was at rest in an upright position. The points of the spine in question were T1 (referred to as point C; T7 (point T) and L1 (point L). At maximum flexion, the angle CTL was recorded via the digitiser. This method was painless and the speediest, plus the standard error factor of the workstation was minimal at 0.03% in the horizontal view and 0.9% in the vertical view (Harrison and Littler, 1991). The position of C, T and L were recorded and remained unchanged in each individual case. A measurement chart was developed in order to position

the probes exactly over the same segment as the previous recording of the spinal movement, thus keeping the distances O-C; C-T and T-L constant for each subject, where O is the occipital protuberance (See Appendix A8 for chart showing calibration of probe positions).

Since the probes were placed on the skin of the patient and not on the actual bone of the spinal column, the tone of the skin overlying the spine had to be taken into consideration. This was assessed each time by placing two strips of adhesive tape next to each other at the position the probe was to be fixed. The patient was then asked to fully flex, and the distance between the two strips during full flexion was measured and recorded. This method revealed how much skin stretch there was under each probe during active flexion. If the distances measured between the two strips of tape were markedly different during each recording, then it would have affected the reliability of the results as any difference in the angles between the probes would be partially due to changed skin elasticity. Thus, only recordings with overall skin stretch that remain similar over the year could be considered accurate as a valid measurement of the angle of flexion.

## 2.2.4 Osteopathic treatment

### 2.2.4.1 Background

The treatment for CFS/ME as seen in the initial chapter includes dietary regimes, with evidence to suggest that an essential fatty acid intake must be normalized in the management of CFS (Gray and Martinovic, 1994). Psychotherapy, physiotherapy, exercise programmes, and antidepressants have all been advocated (Artsimovich *et al.*, 1994). The different treatment programmes each focus on one facet of this complex disorder whether it is chemical, hormonal, environmental or psychological, offering palliative treatment and not a cure.

### 2.2.4.2 Aim of treatment

The main objective of the chosen osteopathic treatment of CFS/ME is to reduce the irritation of the sympathetic nervous system, thus allowing a return to a healthier

homeostatic state within the patient. It is hypothesized by the author that this would be achieved by increasing drainage of toxins from the cerebrospinal fluid via the lymphatics (See Section 5.1). Also the treatment would reduce sympathetic tone by improving structure and overall quality of movement of the lower cervical, dorsal and upper lumbar regions of the spine together with relaxation of surrounding musculature.

The two sympathetic trunks are integrally related to the overall structure of this area. Thus by reducing mechanical irritation, disturbed sympathetic afferent impulses may minimize further helping to stabilize blood and lymph flow.

The therapy lies at the very heart of traditional osteopathic philosophy and practice (Still, 1902). The core theory of this thesis proposes that this system breakdown is central to the disease process of CFS/ME. It is also hypothesised that by rebalancing the neurological equilibrium, one reduces the metabolic disturbance, thus improving the overall symptom picture (Perrin, 1993).

### 2.2.4.3 History and philosophy of osteopathy- an overview

Osteopathy is the knowledge of the structure, relations and functions of each part and tissue of the human body applied to the adjustment and correction of whatever may be interfering with their harmonious operation (Webster, 1928).

Dr. Andrew Taylor Still in Kirksville, Missouri founded osteopathy in the latter part of the nineteenth century as an alternative to the poor quality of medicine practiced at the time. Still called his new system of medicine "osteopathy" from the Greek words for bone *Osteon* and disease *Pathos*. His basic tenet for viewing the body as a machine was religiously based and one of despair, due to the futility of most medication at the time. He formulated his original hypothesis from biblical text. “Let us make man in our image” Genesis Ch1, Verse 26. Taylor Still who was the son of a minister took this verse literally. He postulated that if The Creator is perfect then man must have been made perfect. As he stated “The principles of osteopathy gives us an understanding of the perfect plans and specifications followed in man’s construction” (Still, 1902). Osteopathy teaches that structure governs

function. Thus illness, Still maintained, develops when the perfect structure is out of balance.

It became extremely popular in the American Mid-West and there are now twenty established osteopathic medical schools in the USA, with an enrolment of nearly 10,000 students (AOA, 2002). The first osteopathic college in the UK was The British School of Osteopathy established in 1921 (Hall and Wernham, 2003). Today there are over 3,000 osteopaths in this country registered with the General Osteopathic Council formed by act of parliament in 1998 (OIS, 2000). The profession is now generally accepted alongside other mainstream medical disciplines.

According to the General Osteopathic Council, osteopathy is an established recognised system of diagnosis and treatment, which lays its main emphasis on the structural and functional integrity of the body. It is distinctive by the fact that it recognises that much of the pain and disability, which we suffer, stems from abnormalities in the function of the body structure as well as damage caused to it by disease (OIS, 2000).

One of the major philosophical concepts of osteopathy is that the structure of the body governs the function of the organs within. Osteopaths also work on the principle that a patient's history of illnesses and physical traumas are written into the body's structure (Webster, 1928). It is the osteopath's developed palpatory sense that enables the practitioner to manually diagnose whilst treating the patient. The osteopath's job is to restore a healthy structure of the body and thus its function. The osteopath gently applies manual techniques of massage and manipulation to encourage movement of the bodily fluids, eliminate dysfunction in the motion of the tissues, relax muscular tension and release compressed bones and joints. The areas being treated also require proper positioning to assist the body's ability to regain normal tissue function.

There is a palpable rhythmic motion along the spinal cord and around the brain together with that of normal breathing, which is transmitted to the rest of the body. The accepted hypothesis among most of the osteopathic profession for what is termed the involuntary mechanism or the "cranio-sacral rhythm" is movement through the tension and continuity

of membranes, dura and fascia. The fascia is continuous with the membranes that surround the brain and spinal cord (meninges), thus allowing the different motions (and tension) of the body to be transmitted everywhere. One of Still's students, William Sutherland, noticed that when the bones of a disarticulated skull were viewed in a certain way, they resembled gills of a fish. Therefore, he hypothesised, in 1898, that their shape was designed to allow for movement. He postulated that there was an inherent primary respiratory movement within the cranium bones and of the sacrum between the ilea. This movement corresponds with the motility of the neural tube and the fluctuating rhythm of the cerebrospinal fluid. The average pulsation of this primary respiratory mechanism, as it is also commonly known, is between 7 and12 beats per min in health (Sutherland, 1990).

Sutherland also proposed that the primary respiratory mechanism produces a rhythmic alternation of flexion and extension of structures in the midline. This movement occurs simultaneously with rhythmic external and internal rotation of all paired lateral structures in the cranium (Sutherland, 1990).

#### 2.2.4.4 The lymphatic drainage

The main lymphatic vessels are known to be under sympathetic control (Browse, 1968). The smooth muscle wall of the thoracic duct, when stimulated, produces a wave of contraction aiding lymph drainage into the subclavian vein. This produces a negative pressure along the lymphatics and aids further lymph drainage. The associated peristaltic wave within the normal human thoracic duct was found to be 4 beats per minute with a maximum pressure of around 10-mmHg building up to 50 mmHg if obstructed (Kinmonth and Sharpey-Schafer, 1959).

Sutherland emphasised the importance of the choroid plexus in the chemical exchange between cerebrospinal fluid and the blood, but also stressed the part played by the lymphatics in the drainage of toxins from the neuraxis. Sutherland (1990) said "When you tap the waters of the brain by compressing the fourth ventricle see what happens in the lymphatic system. Visualise the lymph node that is holding some poison that has gathered there, changing the constituency before the lymph is moved along into the venous system"

"We strike at the source of life and death when we go into the lymphatics" (Still, 1899). Andrew Taylor Still discussed the importance of examining disturbed fluid motion in the head, in the pathogenesis of many symptoms such as headaches, enlarged tonsils, dizziness and loss of memory, all associated with CFS/ME. He emphasised that alongside good blood supply it was equally important to have perfect drainage (Still, 1902).

Sutherland (1990) postulated that each facial sinus has one or more other bones which help drain the mucus, produced in the goblet cells of the sinus epithelial lining, by a gentle pumping action. This facilitates the wafting action of ciliated epithelium, which forces the mucus into the nasopharynx. When mechanical or other forces damage this mechanism the sinus is less able to drain its mucus. As a result the mucus pools, thickens and makes the subject prone to infection. The nasal mucosa becomes continually inflamed with an abundance of purulent mucus and associated enlargement of adenoids and tonsils. Lymphatic vessels in the submucosa of the nasal sinuses are the initial recipients of the drainage of CSF through the cribriform plate (Knopf and Cserr, 1995). As osteopathy's founder stated over a century ago "Harmony only dwells where obstructions do not exist" (Still, 1899).

It is the above pathway that the author believes to be compromised mechanically as part of the common pathogenesis in CFS/ME. Mechanical dysfunction such as this can be detected by palpation and can be released by gentle pressure techniques applied to the cranium and the spine. As early as the1890's, Still noted "The lymphatics are closely and universally connected with the spinal cord and all other nerves, and all drink from the waters of the brain" (Still, 1902). From the earliest days of osteopathy the importance of good lymphatic drainage in the thoracic duct has been seen as paramount to sustain health. Still himself wrote: "At this point I will draw your attention to what I consider is the cause of a whole list of hitherto unexplained diseases, which are only effects of the blood and other fluids being prohibited from doing normal service by constrictions at the various openings of the diaphragm. Thus prohibition of the free action of the thoracic duct would produce congestion" (Still, 1902).

At present there is no means of measuring the patient's cerebrospinal fluid's drainage into the lymphatic ducts although it is safe to assume that it is directly influenced by the thoracic duct pump. Palpation of the CFS/ME patients revealed a notable reduction in the involuntary mechanism compared with the healthy group.

### 2.2.4.5 The scientific validity of osteopathy and other manual therapies

The author, being a fully trained osteopath of almost twenty years experience, may be more familiar with osteopathic manual techniques as compared with chiropractic and physiotherapy personnel. However there is no reason why trained manual therapists from any discipline cannot treat CFS/ME using similar methods. In fact osteopathy and chiropractic share common roots. Palmer established chiropractic in the late 19th century in the United States after meeting with Still, the founder of osteopathy. The therapies remain relatively comparable with the term "manipulative therapy" referring to both osteopathy and chiropractic. However these two established professions do not hold a monopoly in manipulation. Many physiotherapists and massage therapists also use manipulative techniques similar to those of chiropractors and osteopaths. Although chiropractic is known more for its specific and sometimes quite forceful manipulative procedures of the spine, there has emerged a relatively recent branch of chiropractic, the McTimoney School, which has developed some of its own gentle manipulative techniques that do not place as great an emphasis on high velocity thrusts as do osteopathy and mainstream chiropractic.

Some osteopaths also practise a technique known as cranial osteopathy or craniosacral therapy. Practitioners place their hands on the cranium and sacrum and gently handle the bones of the skull, feeling for subtle rhythmic pulsations of the cerebrospinal fluid, and attempting to correct disturbances in the neuromuscular system. There are some therapists, usually known as craniosacral therapists, who use similar techniques but who do not have an osteopathic background.

Both osteopathy and chiropractic were originally regarded as complete systems of medicine. Early chiropractors believed that most diseases could be treated by treatment of misalignments of the spine. Present-day practitioners concentrate primarily on musculoskeletal disorders. Low back pain is the most common presenting complaint. Guidelines from the Royal College of General Practitioners recommend physical therapy (any of the manipulative techniques) within six weeks of the start of persisting uncomplicated back pain.

There is considerable evidence from randomised controlled trials on the effectiveness of spinal manipulation in the region of the back and neck pain. Although this evidence is largely positive, it has been criticised for failing to exclude non-specific effects of treatment.

In the best known UK trial 741 patients with low back pain were randomised to chiropractic or hospital outpatient-care (Meade *et al.*, 1995). In both groups the treating practitioners were free to treat patients as they saw fit. The authors concluded, "Chiropractic almost certainly confers worthwhile, long term benefit." However Koes *et al.* (1996) disagree with some measured outcomes in that study such as pain and disability, since the self-score system used by patients was unblinded.

In one earlier trial that did involve blinded assessment of outcome, patients with back or neck pain were randomised to routine general practitioner care, placebo (deactivated heat treatment), physiotherapy, or manipulation (Koes *et al.*, 1991). Physiotherapy and manipulation were superior to placebo and general practitioner care after six weeks, and manipulation was superior to physiotherapy at a one-year follow up (Koes *et al.*, 1992).

In addition to effects on back and neck pain, randomised trials have also indicated that manipulative treatment is beneficial for headache, including migraine (Tuchin *et al.*, 2000). However, the numbers of studies are small, so further work to confirm this result is needed. There is little or no reliable evidence of beneficial effects for many of the other musculoskeletal conditions that are commonly treated. Apart from dysmenorrhoea, for which a small number of trials have shown a positive effect, current evidence suggests that

manipulative therapy does not benefit patients with problems related to smooth muscles or viscera, such as asthma and hypertension. There has been little research on cranial osteopathy or McTimoney chiropractic.

Adverse effects of osteopathy and chiropractic if applied by a trained practitioner are few, but stroke and spinal cord injury has occurred after cervical manipulation. Estimates of such severe adverse events vary widely, ranging from 1 in 20 000 patients undergoing cervical manipulation to 1 per million procedures. Osteopathic and chiropractic professions have shown greater appreciation of the risks of cervical manipulation, and it is possible that improved practice is leading to a reduction in the rate of severe complications (Koes *et al.*, 1992, 1996; Balon *et al.*, 1998; Meade *et al.*, 1995, 1990)

There has been a promising pilot study providing evidence that spinal manipulation is more effective than acupuncture or non-steroidal anti-inflammation drugs (NSAIDs) for chronic spinal pain syndromes (Giles and Muller, 1999). Furthermore a panel of 20 leading experts on low back pain was in favour of osteopathy and chiropractic for acute uncomplicated low back pain (Ernst and Pittler, 2000). Spinal manipulation has also been shown to help in non-mechanical problems e.g. migraine (Tuchin *et al.*, 2000).

### 2.2.4.6 Stages of treatment

The specific osteopathic techniques used in the treatment protocol developed by the author are based on standard procedures used by trained osteopathic practitioners (Stoddard, 1982; Hartman, 1983).

The manual treatment of each CFS/ME subject consisted of the following stages:

1. Effleurage to aid drainage in thoracic and cervical lymphatic vessels.

2. Gentle articulation of thoracic and upper lumbar spine, plus the ribs. This was achieved by both long and short lever techniques.

3. Soft tissue massage of the paravertebral muscles, the trapezii, levator scapulae, rhomboids and muscles of respiration.

4. High and low velocity manipulation of the thoracic and upper lumbar spinal segments using supine and side-lying combined leverage and thrust techniques.

5. Functional techniques to the suboccipital region and the sacrum.

6. Stimulation of the cranio-sacral rhythm by functional-cranial techniques.

Exercises were also prescribed to improve the quality of thoracic spine mobility, and to improve the coordination of the patient.

The treatment schedule listed below was the protocol followed throughout the year. It altered slightly depending on the physical state of the patient and on the symptom picture at that particular stage in their therapy.

#### 2.2.4.6.1 Effleurage to aid drainage in thoracic and cervical lymphatic vessels

Congested lymph and oedematous changes that often occurred was relieved by effleurage, which is a method of massage involving stroking motions along the surface of the body. The gentle strokes were carried out rhythmically towards the subclavian region, overlying the subclavian veins which drain all the lymph fluid into the blood circulation. Effleurage stimulated the lymphatic drainage through direct routes into the thoracic duct and hence into the venous return (see Fig. 10). Care was taken to avoid stimulating drainage into the axillary lymph nodes which were prone to swelling and congestion in CFS/ME sufferers. It is hypothesised that the more direct route forced a high pressure within the smaller parasternal vessels which created enough force within the thoracic duct to alleviate the back-pressure and return to a healthy drainage of toxins into the venous return.

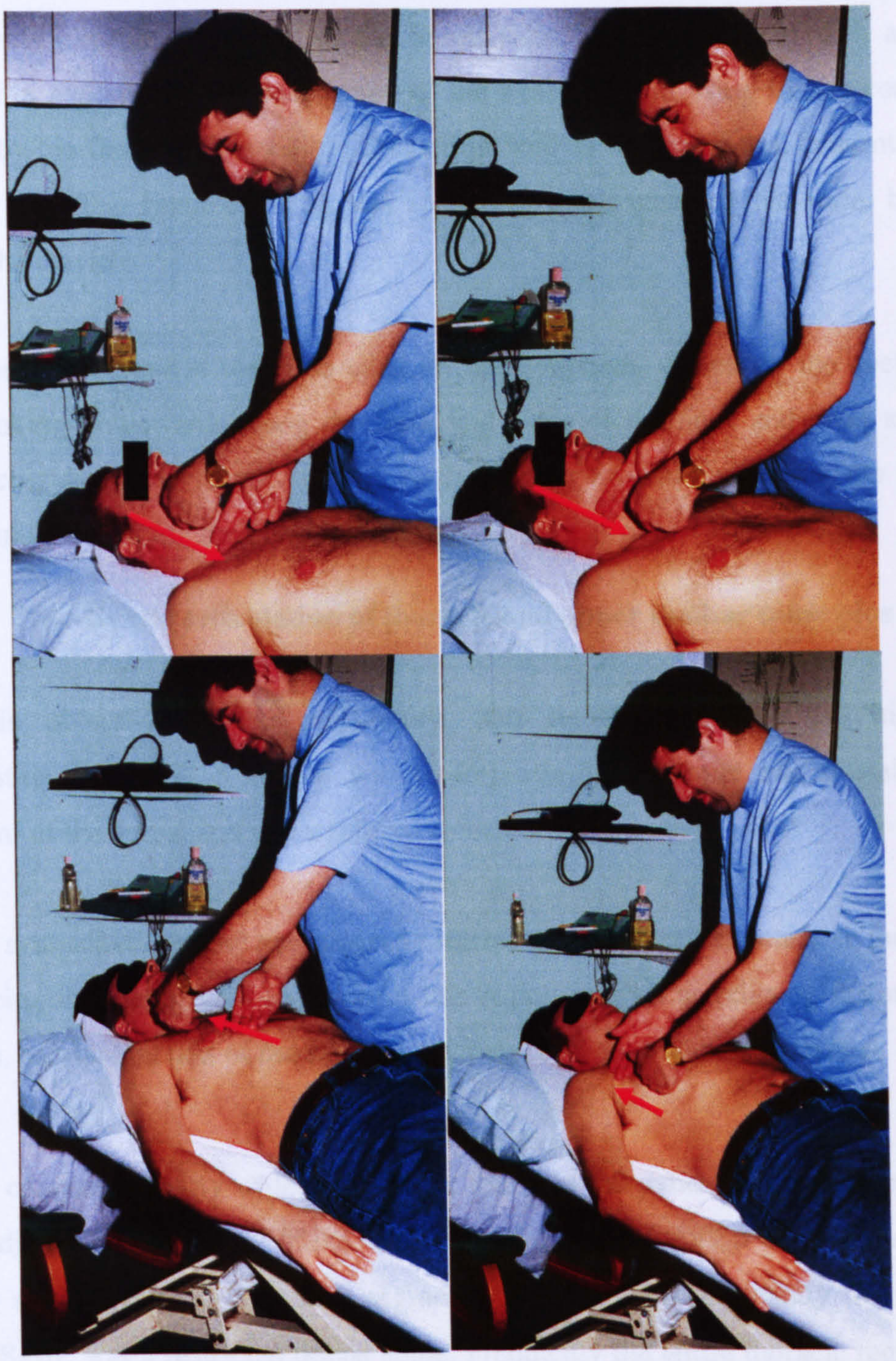


**Figure 10 Effleurage down neck and up chest to clavicle**

The red arrows show the direction of the massage technique which was always towards either clavicle on both sides. This is the region overlying the drainage of lymphatic fluid from the right lymphatic duct and the thoracic duct into the right and left subclavian veins respectively.

With female patients effleurage to the breast tissue was carried out with a chaperone present after explaining the exact nature of the treatment and using further consent forms supplied by the General Osteopathic Council as well as the initial trial consent forms (See appendix A4). The gentle stroking was applied upwards covering the entire breast tissue towards the clavicle

The effleurage technique was also used on the lymphatic vessels of the neck, head and back, stroking downwards along the back and sides of the neck and head and upwards along each side of the thoracic spine. Each stroking motion finished at the level of the subclavian vein creating the pressure mentioned above.

#### 2.2.4.6.2 Gentle articulation of thoracic and upper lumbar spine plus the ribs

The main objective of the articulatory, soft tissue techniques and high velocity manipulation (stages 2, 3 and 4) was to improve the structure and overall quality of movement of the dorsal and upper lumbar spine.

The two sympathetic trunks are integrally related to the overall structure of the area. Thus by reducing the mechanical irritation at this region as well as relaxing disturbed afferent impulses, the dysfunction of the sympathetic nervous system can be corrected.

In cases of hypermobility which was rarely found in the patient's thoracic spine, mobility of the adjoining areas of the spine was improved by articulation and manipulation. This took the strain off the hypermobile segments. What was predominantly found in patients with CFS/ME was a restricted dorsal spine. Frequently the entire thoracic region was stiff, but occasionally only a few segments were affected.

Treatment to increase mobility of the spine can take many forms (Stoddard, 1982; Hartman, 1983). The general articulatory manoeuvres employed were short lever mobilisation using gentle pressure on the pars articularis and spinal processes, plus long lever rhythmic stretching of the dorsal and lumbar spinal segments using the upper and lower extremities

for the appropriate leverage. All the articulatory techniques were slowly and gently applied with minimal force to avoid irritating spinal inflammation and to reduce any reactive spasm from the surrounding musculature.

This method was also carried out with the patient lying supine, but mostly the patient lay on the side to allow a gentle stretch of periscapular and paravertebral muscles together with gentle massage upwards along the spine to improve lymphatic flow. This was often combined with gentle stretch of the ribs performed by holding the patient's arm with one hand, fixing the ribs with the other hand, and gently moving the held arm upwards stretching the thorax above the fixed rib. Combined stretch and massage, using the patient's arm as a long-lever produced excellent results, with movement of the ribs also increased by articulatory stretch techniques (see Fig. 11).

To remedy the problems caused by hypermobile joints, as was the case of restricted joints, the first task was to reduce any possible inflammation present at the damaged segments. This could have been achieved in various ways. Most practitioners would prescribe anti-inflammatory drugs. However, contrast bathing was deemed preferable as it has no toxic side effects.

The hot compress usually consists of a warm water bottle. "Warm" and not hot, as too hot a compress may have scalded the patient's skin. The "cold" was close to freezing point; however some CFS/ME patients can not tolerate extreme temperatures and so in those cases the frozen pack was wrapped with a cover. Frozen peas, which easily mould around the back, were used although special cold compress packs which remain soft even when frozen were found to be more suitable. Clinical experience of the author has shown that the sequence of contrast bathing that seemed to give the best results in reducing the inflammation in CFS/ME was as follows:

COLD - 3 minutes }

WARM - 1 minute }

COLD - 1 minute } TOTAL 10 MINUTES

WARM - 1 minute }

COLD - 1 minute }

WARM - 3 minutes }

This process has no adverse side effects, and so was safe to be used as many times as required. Applications of at least three times a day to the upper thoracic region was the recommended dose if there was inflammation in the neck and shoulders (or there were cerebral symptoms) and the lower thoracic area when the abdominal or lower extremities were affected. The main advantage of contrast bathing over anti-inflammatory drugs is that it worked quickly and directly on the affected area. Even when there was no palpable or visible inflammation, shown by heat and redness, contrast bathing to improve circulation in the thoracic region, was still advised.

**2.2.4.6.3 Soft tissue massage of the paravertebral muscles, trapezii, levator scapulae, rhomboids and muscles of respiration.**

Generally the massage technique for the relaxation of the aforementioned muscle groups took the form of gentle longitudinal and cross-fibre stretching (Hartman, 1983.) Non-perfumed sweet almond oil was used as it is the most common used base oil in massage and seems to be fairly hypoallergenic.

With the patient lying on the side, paravertebral muscles, primarily the dorsal erector spinae, were manually stretched using direct longitudinal pressure up to a level parallel with the first thoracic vertebra. Combined with long lever stretching via movement of the patient's arm and shoulder joint, this method has the added advantage of increasing rib movement and stimulating deep lymphatic drainage from the spine (see Fig. 11).

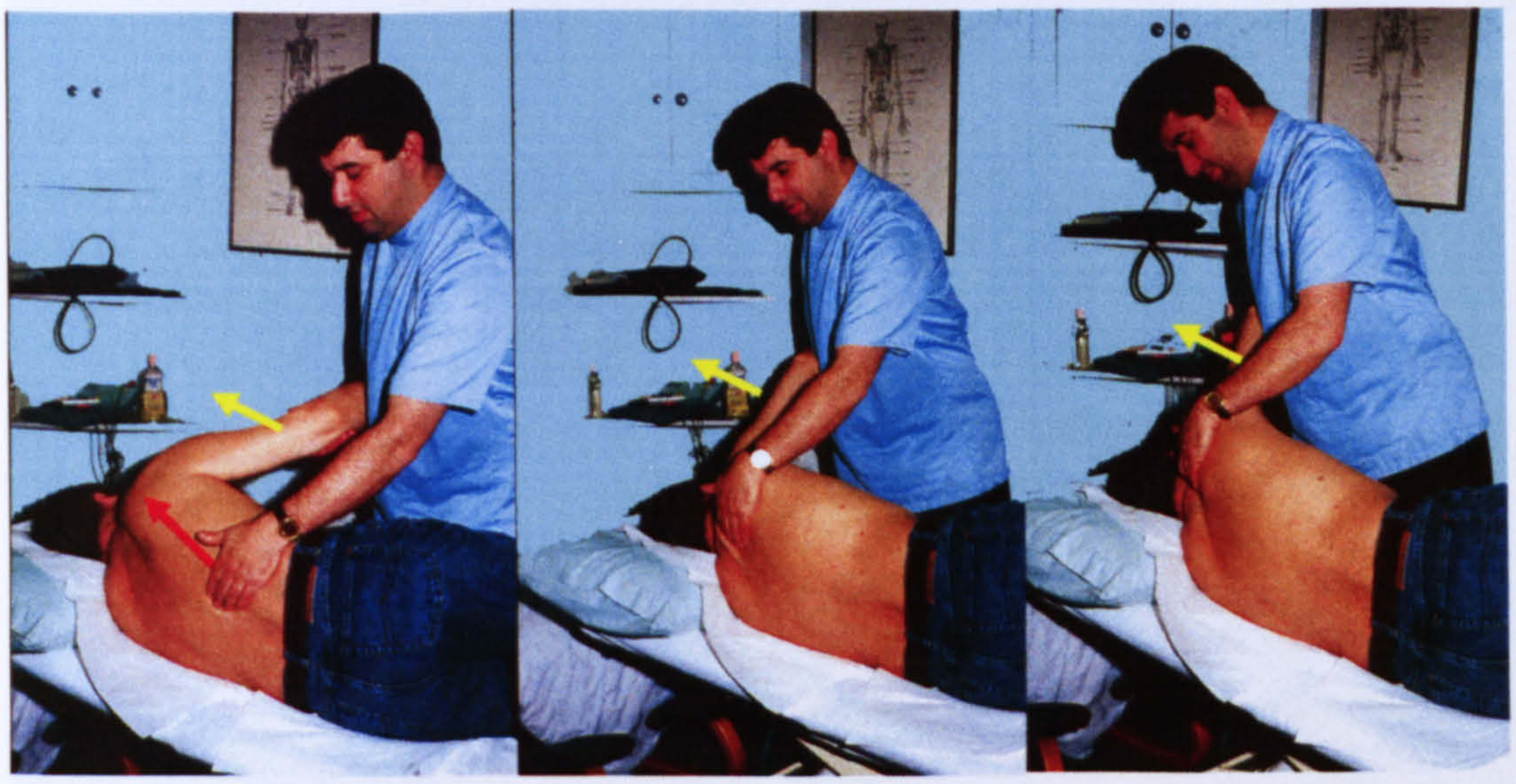


**Figure 11 Combined articulation, soft tissue stretch and paraspinal effleurage**

The method illustrated is a combination of three soft tissue techniques: Long lever stretch of the intercostals, using the patients arm as a lever; direct longitudinal stretch of the dorsal erector spinae and with the finger tips, effleurage to the paravertebral lymphatics. The red arrow illustrates the direction of the massage; the yellow arrows show the direction of movement of the patient's arm.

The patient was not usually in a prone position. However if it was necessary for the patient to lie down prone their face was placed into a breathing hole to avoid unnecessary strain on the neck. The patient was positioned on to the side as soon as possible to carry out the soft tissue work in this healthier position, whilst keeping the head level and knees apart with the aid of pillows Soft tissue stretching commenced with both cross fibre and longitudinal stretch applied rhythmically to the cervical, dorsal and lumbar erector spinae (see Fig. 12).

Treatment was also given to relax the trapezii (see Fig. 12) and periscapular muscles e.g. rhomboids, as well as any other hypertonic back and shoulder muscles. Besides stretching, occasionally inhibition or functional techniques were used to reduce the tone of the tightened musculature (see Fig. 16)

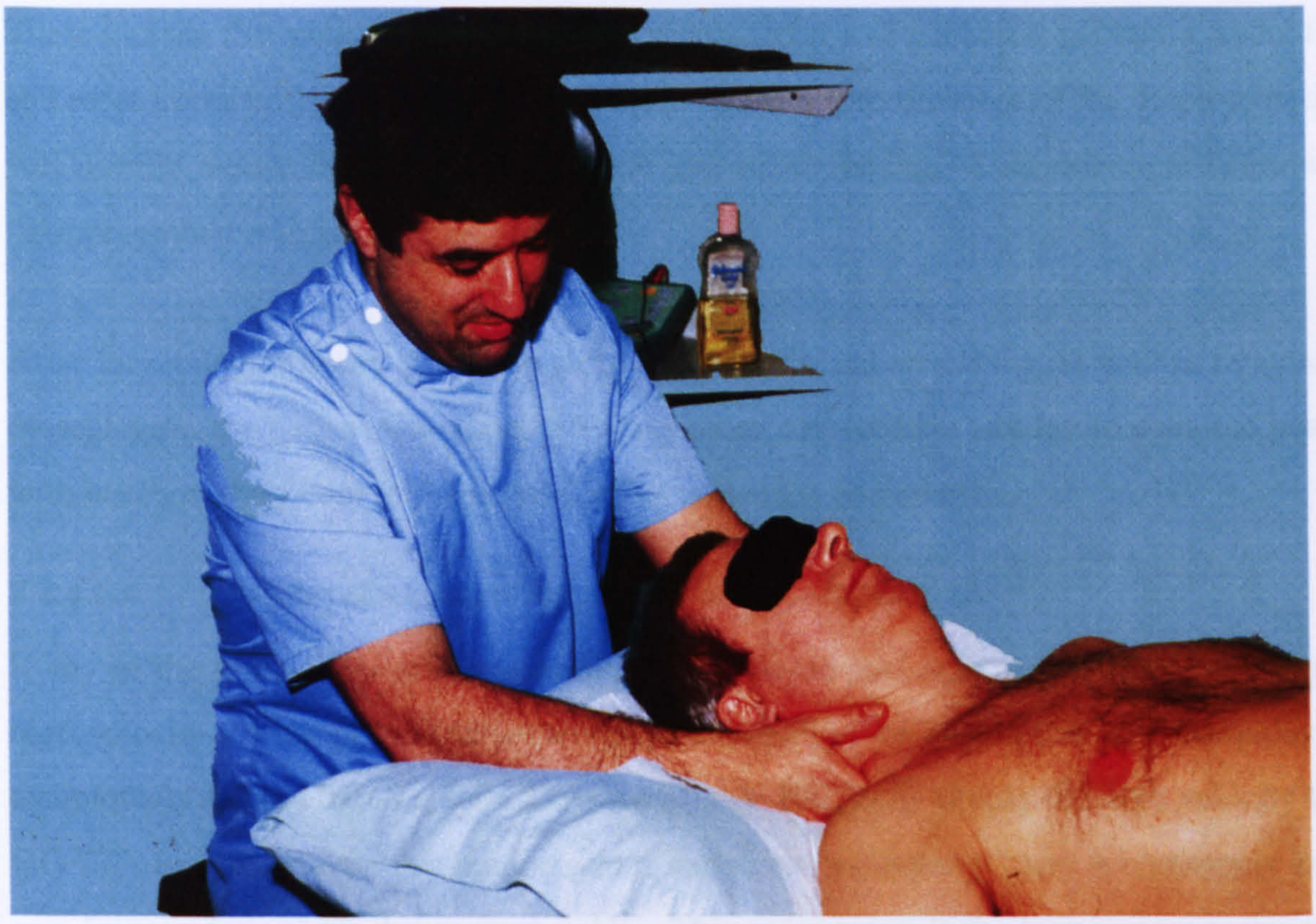


**Figure 12 Cross fibre stretching of lower neck and shoulders**

This technique involves a slow rhythmic kneading action applied to across the fibres of the lower cervical erector spinae, trapezii and levator scapulae.

After increasing movement of the restricted spine and relaxing the surrounding musculature, an attempt to improve the respiratory mechanics was undertaken. This is important in CFS/ME patients, since the amount of oxygen in the body affects the chemical content of the body, and also has a direct affect on general functioning of the body's tissues. Reduced oxygen will produce greater fatigue in the patient and will aggravate the symptoms. By improving the mechanics of respiration in the rib-cage, one increases the lung capacity during inspiration thus raising the oxygen intake of the patient.

Although increasing spinal mobility and relaxing paravertebral muscles will also enhance movement of the ribs, there are specific muscles-of-respiration that should be treated to improve the respiratory mechanics.

These include the intercostal muscles, serratus anterior and posterior, pectorals, abdominals and most importantly the diaphragm. Gentle inhibition to the edge of the diaphragm dome will usually reduce the tone of the muscle and aid breathing. This technique is known as "diaphragmatic release".

After increasing mobility of the thorax by articulation and stretching, as well as relaxing the musculature, the patient was usually feeling more comfortable and lay in a supine position with knees slightly bent in readiness for the next stage of therapy.

#### 2.2.4.6.4 High velocity-low amplitude manipulation

If any of the joints were severely immobile, it proved necessary to increase movement by high velocity low amplitude thrust techniques (see Figs. 13,14 and 15). In Osteopathy, this technique is called High Velocity-Low Amplitude HVLA or simply the high velocity thrust (HVT). In Chiropractic this manoeuvre is called an "adjustment" and is commonly known as a "manipulation" by the general public. This manoeuvre is the best known technique in the osteopath's armoury and involves a short, sharp motion usually applied to the spine. This procedure is designed to release structures with a restricted range of movement. There are various methods of delivering a high velocity thrust. Chiropractors are more likely to push on vertebrae with their hands, whereas osteopaths tend to use the limbs to make levered thrusts. That said, osteopathic and chiropractic techniques are converging, and much of their therapeutic repertoire is shared. This technique may produce a 'cracking' sound.

The HVTs can be achieved with the patient lying prone, but it was preferable and safer to turn the patient onto their back and manipulate them in the supine position. Vertebral joints in some patients appeared slightly fused, and so strong manipulation was avoided thus averting damage to the bone.

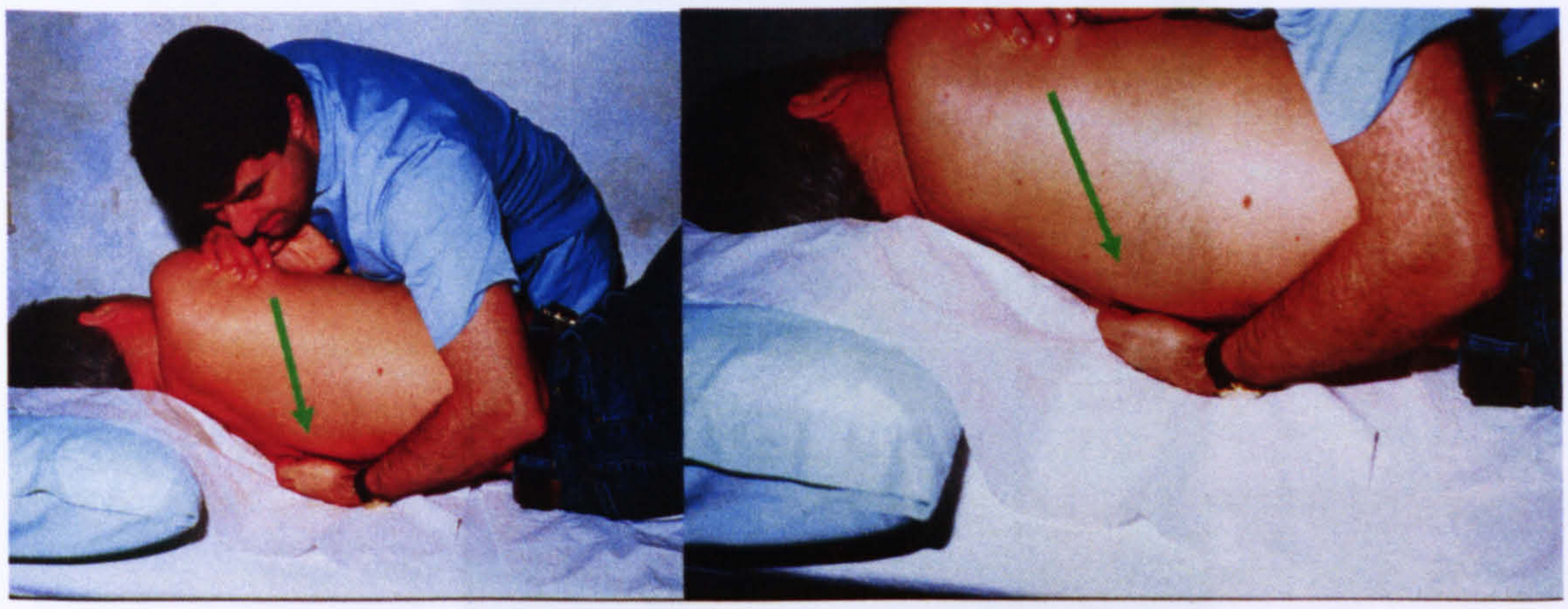


**Figure 13 Combined leverage and thrust of mid thoracic vertebrae**

The author's left hand is positioned in a loose fist to gap the facet joints. When the tension has built up by positioning the patient's upper spine in a flexed and rotated position, a fast but gentle pressure is applied through the direction of force as illustrated by the arrow.

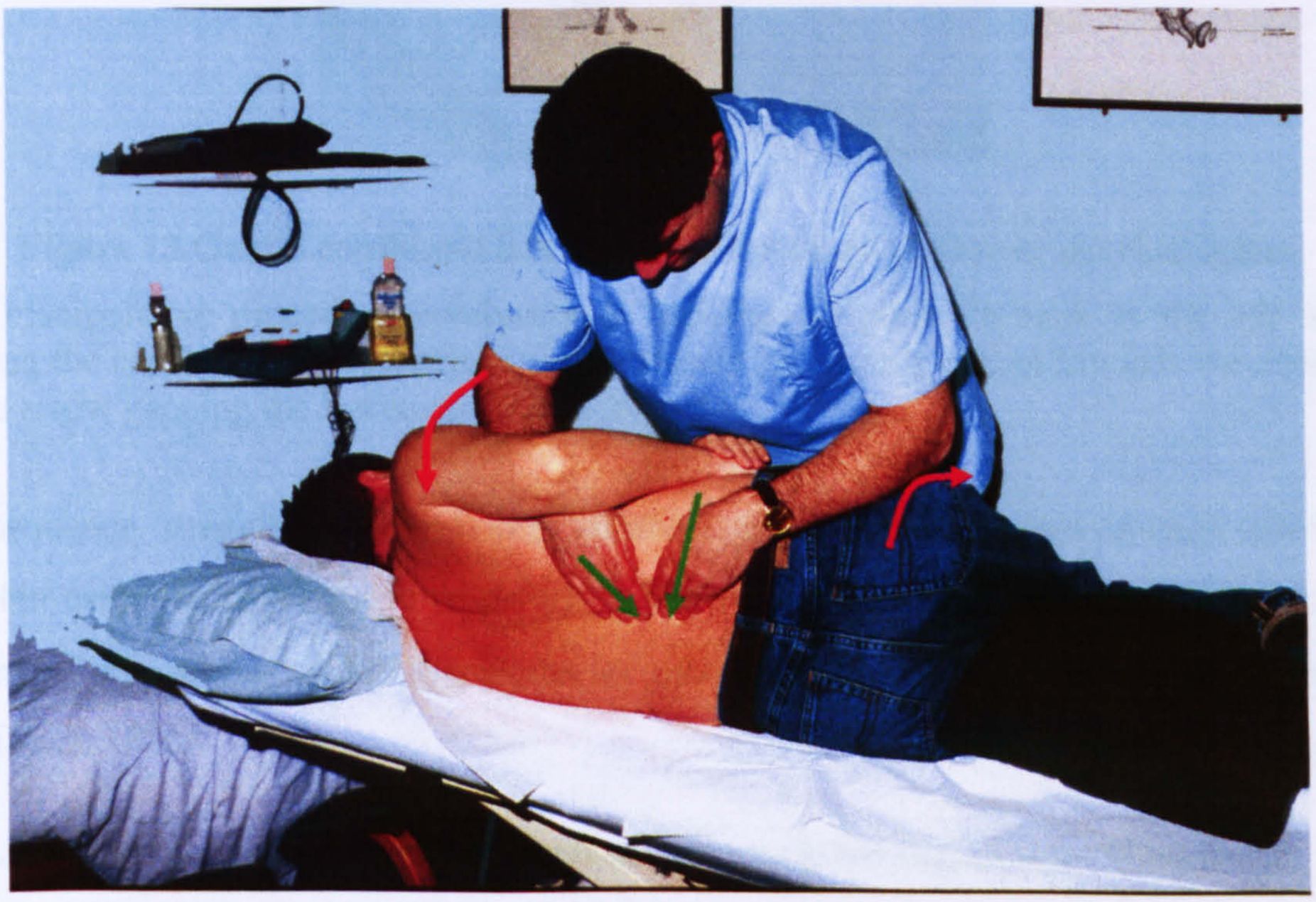


**Figure 14 Combined leverage and thrust on the upper lumbar spine**

→ direction of rotation; → direction of force

The upper lumbar vertebrae were gently manipulated, gapping any restricted facet joint.

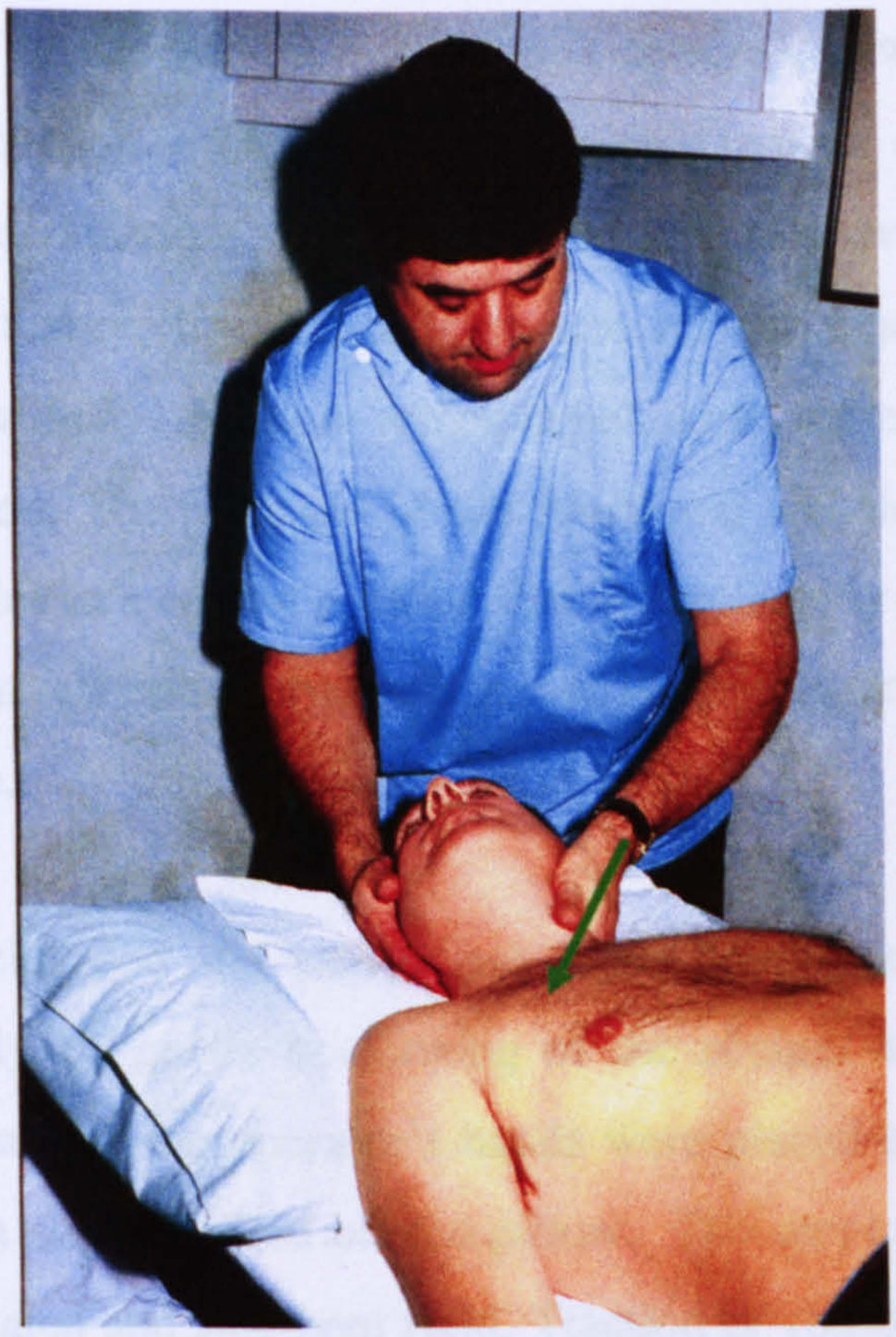


**Figure 15 Gentle combined leverage and thrust on the lower cervical spine**

This manipulative procedure involves side bending the patient's neck to the left whilst rotating the cervical spine towards his right. Gentle pressure is placed towards the direction of the arrow gapping the lower cervical facet joints.

The sequence, strength, and duration of all above techniques was based on each individual case but care was taken not to over-manipulate especially in the lower cervical region, as this may have worsened the symptoms by over-stimulating somatico-sympathetic reflex arcs (Korr, 1978).

#### 2.2.4.6.5 Functional techniques to the sub-occipital region and the sacrum.

It is important when one treats posturo-mechanical strain of the spine to balance the sub-occipital and lumbosacral segments. Any abnormal kyphosis, lordosis or scoliosis will alter muscular tone along the spinal column and thus place extra load on the uppermost section and base of the spine. Similarly positional alterations of the spinal poles will affect the overall mechanics of the entire spine. Osteopaths and chiropractors may also use an affective "fine-tuning" procedure in these regions known as " functional techniques," If

during subtle movement of the spine a restriction is detected, however slight, the back is held at the point of restriction until a release of muscle tension occurs. Techniques like these are based on an understanding of subtle neuromuscular behaviour, which conforms to mainstream osteopathic theory. In practice, they also rely on finely developed palpatory skills. As mentioned previously, the main principle behind any osteopathic treatment is that structure governs function. The principle of the functional technique is that by placing a joint or a group of muscles in a certain position that is functionally suited for that particular bodily part, the result is a relaxation of tissues and an overall improvement in muscular and fascial tone in the region.

The sub-occipital muscles and the pelvic and lower lumbar muscles can be relaxed efficiently and painlessly by gentle positioning of the occiput and sacrum respectively. With the patient lying supine the operator's hands were placed at each side cradling the occiput, which was then slightly lifted off the pillow. The cervical spine was then gently extended and slowly rotated and side-bent right. Traction or compression was then applied and by asking the patient to breathe deeply, one was able to utilise exhalation as a relaxation tool. There was a fixed position whereby palpating the muscular tone just beneath the occiput, using the finger tips, one was able to feel the point of maximum relaxation for the sub-occipital muscles. This position was held for a few seconds resulting in a reduction of tone in this muscular group.

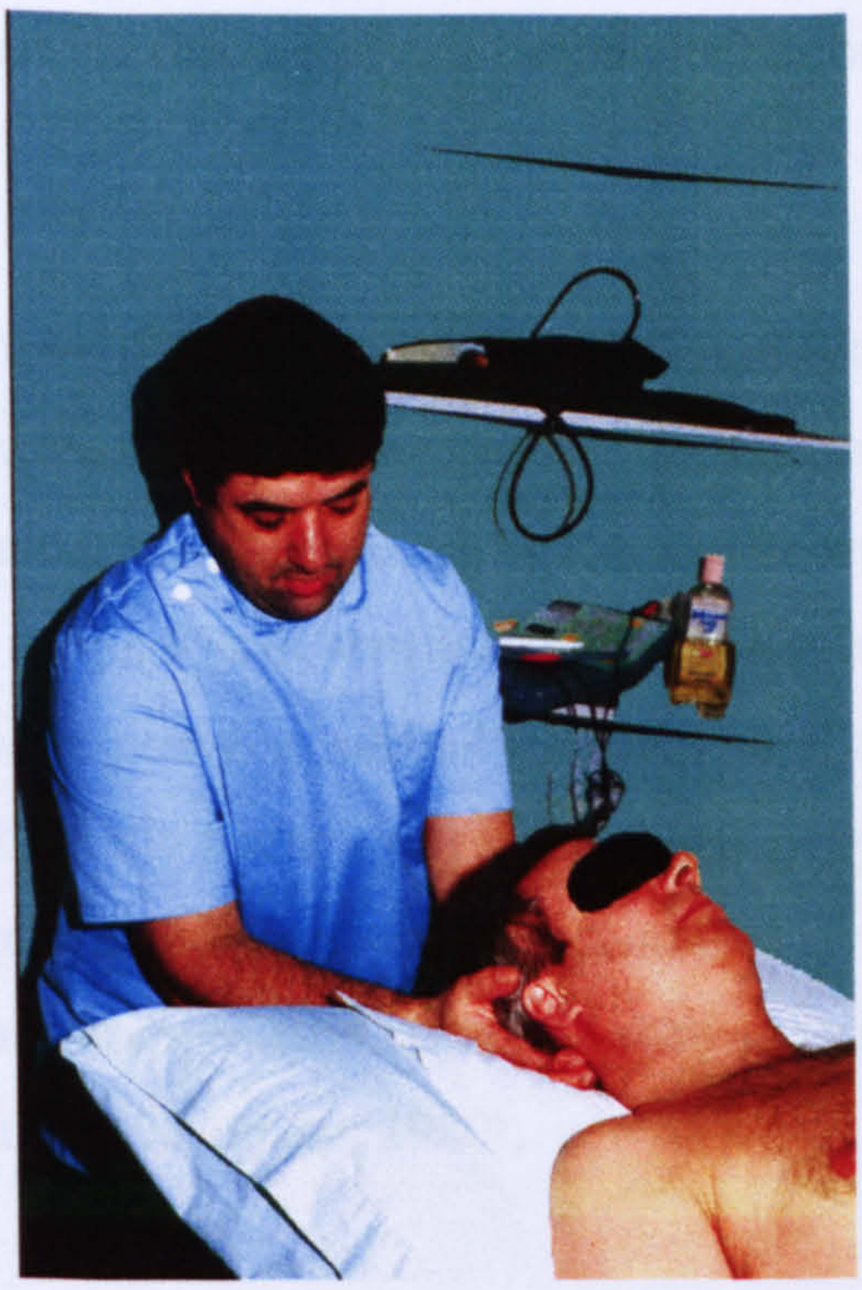


**Figure 16 Functional technique to the suboccipital region**

With the patient lying supine the operator's hands were placed at each side cradling the occiput, which was then slightly lifted off the pillow and held in a fixed position to produce comfort and relaxation of the tissues in the upper cervical region.

The same technique was applied to the pelvic and lower lumbar region by cradling one hand under the patient's sacrum and palpating the muscular tone in the lumbar sacral region.

#### 2.2.4.6.6 Treatment to the cranio-sacral rhythm

Stage six commenced near the end of each consultation (see Fig. 17). This was found to be very effective at restoring energy and improving the cognitive ability of the patient and was thus extremely useful in the overall treatment.

The fluctuation of the slow wave previously described by Sutherland is known as the cranial rhythmic impulse CRI. The CRI has a flexion (inspiration) phase and an extension (expiration) phase faintly changing the shape of the ventricles (Lay, 1997). Similar to the affects of the thoracic duct pump influencing the entire lymphatic system (Kinmonth,

1982), the CRI is transmitted via fascia and can be palpated throughout the body (Upledger and Vredevoogd, 1983).

The fourth ventricle lies above the pons and below the cerebellum and between the lateral peduncles. The dorsal surface of the cerebellar hemispheres lies adjacent to the supraocciput. The main cranial technique used by the author was a procedure known as a CV4 (i.e. the compression of the fourth ventricle). This compression is achieved by gentle force applied with both hands pressing medially at the lateral angles of the occiput. This causes the occiput to slightly tilt inward increasing tension on the tentorium drawing it firmly on to the cerebellum which as a consequence, moves down on the roof of the pons and medulla. This downward compression coincides with an upward force on the pons and medulla from the brachium pontis (Meyer, 1980).

By using the CV4 technique, the volume within the fourth ventricle is reduced, forcing the cerebrospinal fluid out through the aqueduct of Sylvius. The foramina of Lushka and Magendie allow drainage into the ventricle and subarachnoid spaces with reabsorption into the venous return via arachnoid villi (See Fig. 32) (Magoun, 1966).

It is hypothesised that CSF drainage through the cribriform plate and down the spine will also be enhanced by the above procedure. Thus it plays an important role in the overall treatment. Care was taken not to over-stimulate the cranial rhythm with too long or forceful a treatment. After resuming a seated position the patient was advised to remain sitting for a moment and not to stand abruptly. This was aimed at reducing dizziness due to the neural mediated hypotension commonly found in CFS/ME (Werbach, 1998).

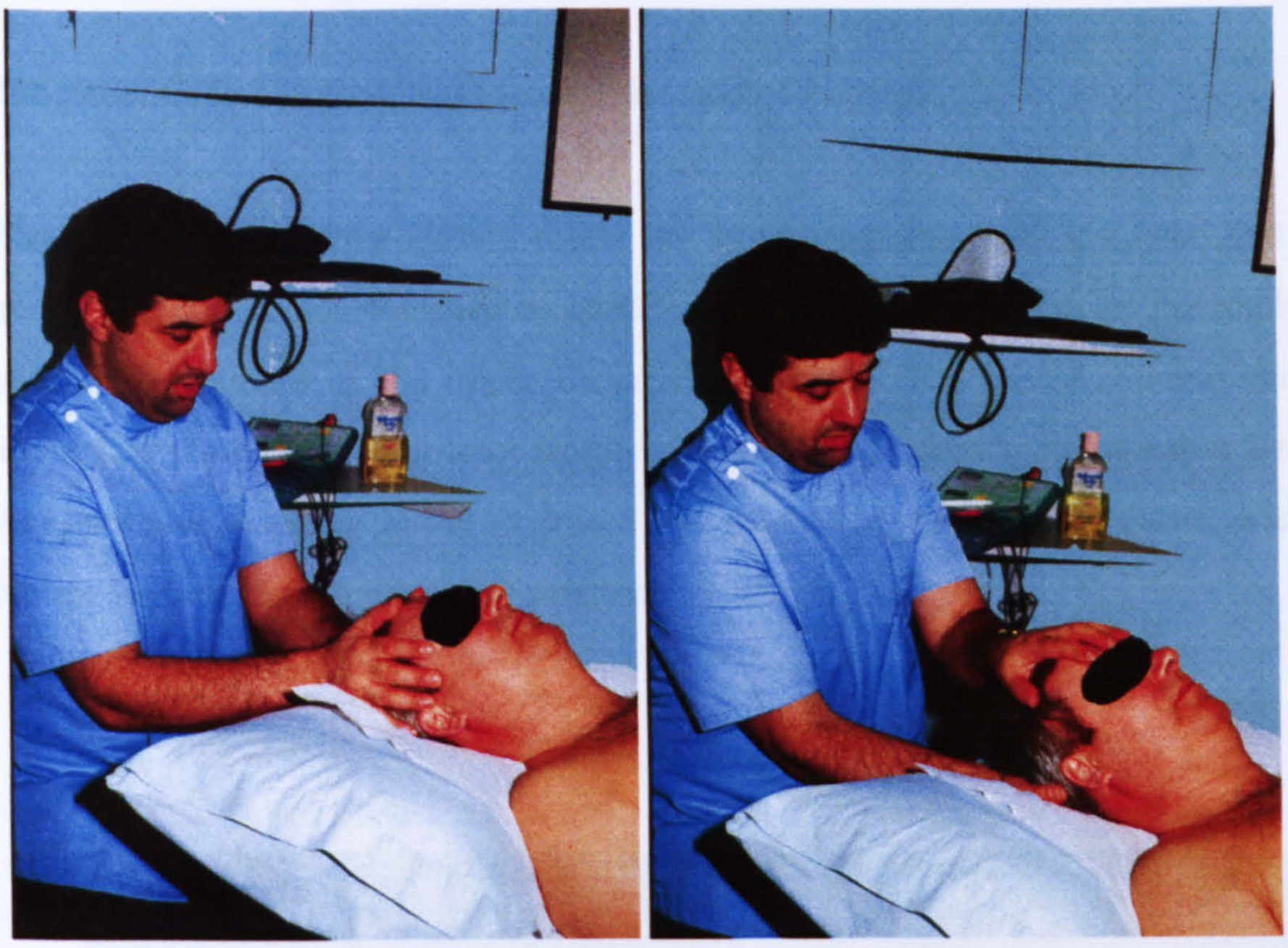


**Figure 17 Cranial treatment**

The operators hand is placed in two different positions cradling the head laterally and antero-posteriorly. The cranial procedure involves very gentle pressure and movements that are very minimal.

## 2.2.5 Other advice to patients

Osteopathic treatment is not synonymous with manipulation. Many treatments of numerous conditions were found to be insufficient if they relied on manual therapy alone (Stoddard, 1982). As in standard osteopathic practice, advice was also given to the patient group to help improve their general health.

### 2.2.5.1 Dorsal rotation exercise

Manual treatment of the patient improved function of the thorax and the spine especially when enhanced by routine mobility exercises. An effective exercise prescribed to improve and maintain the quality of movement of the dorsal spine was as follows (see Figs 18, 19 and 20):

The patient is seated.

The patient's hands are placed around the side of the neck.

The patient should then slowly rotate the trunk, together with the head and neck. This gentle rotation is not designed to stretch muscles and joints, but to gradually and subtly increase movement of the upper thoracic vertebrae. The arc of rotation should only be about forty five degrees in total from right to left This should be repeated five times each way, without stopping in the middle. The movement must be rhythmic, with the patient feeling relaxed during the entire process.

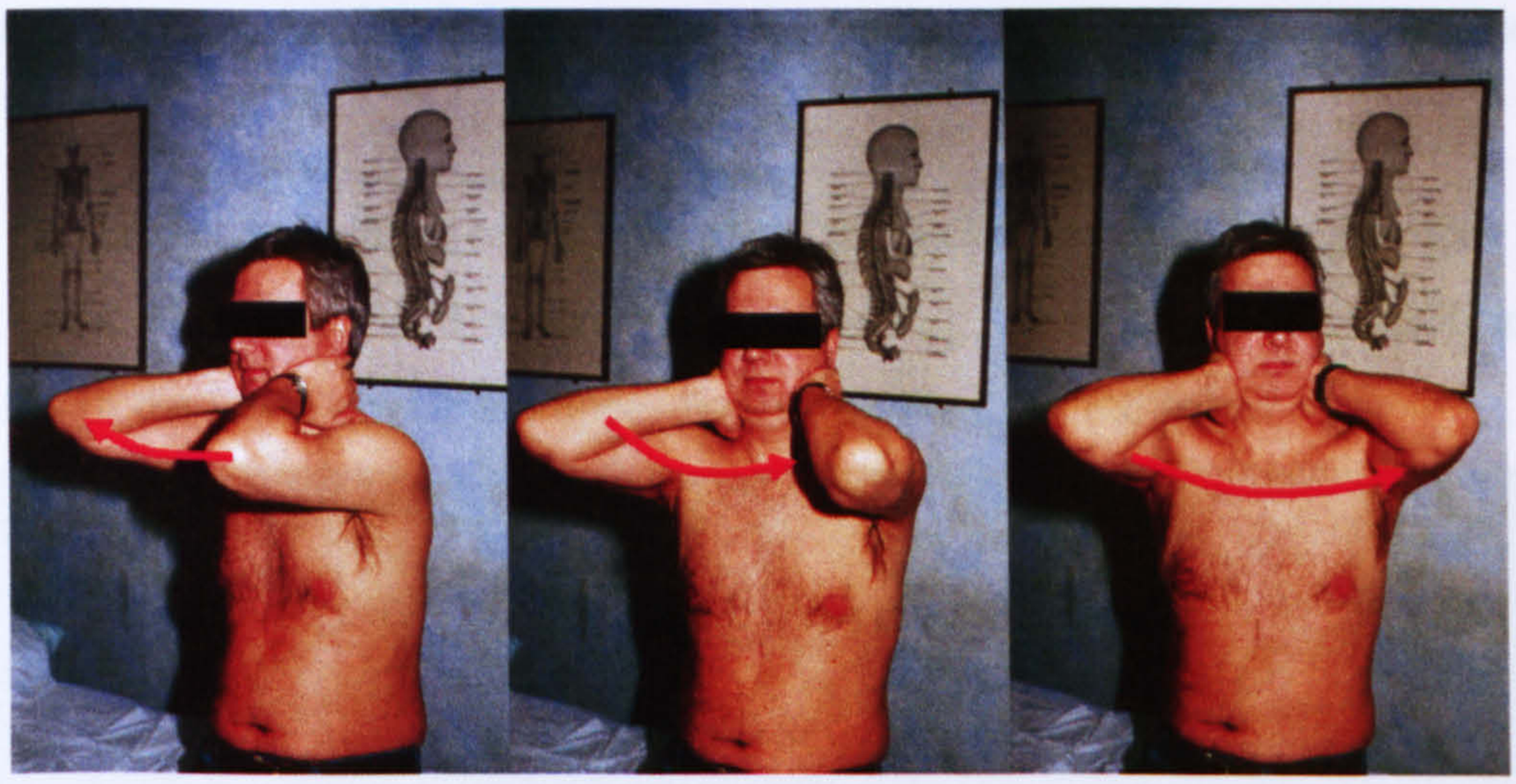


**Figure 18 Upper thoracic rotation exercise**

The patient slowly rotates his upper back 5 times each way, through an arc of 45 degrees whist sitting. When holding the side of his neck, this rotation gently stretches the upper thoracic spine.

Patients should then cross their arms and hug their shoulders with their hands. The movement to the right and left is then repeated five times each way as above, making sure that the head, neck and shoulders all move in unison. This part of the exercise encourages movement in the middle section of the thoracic spine.

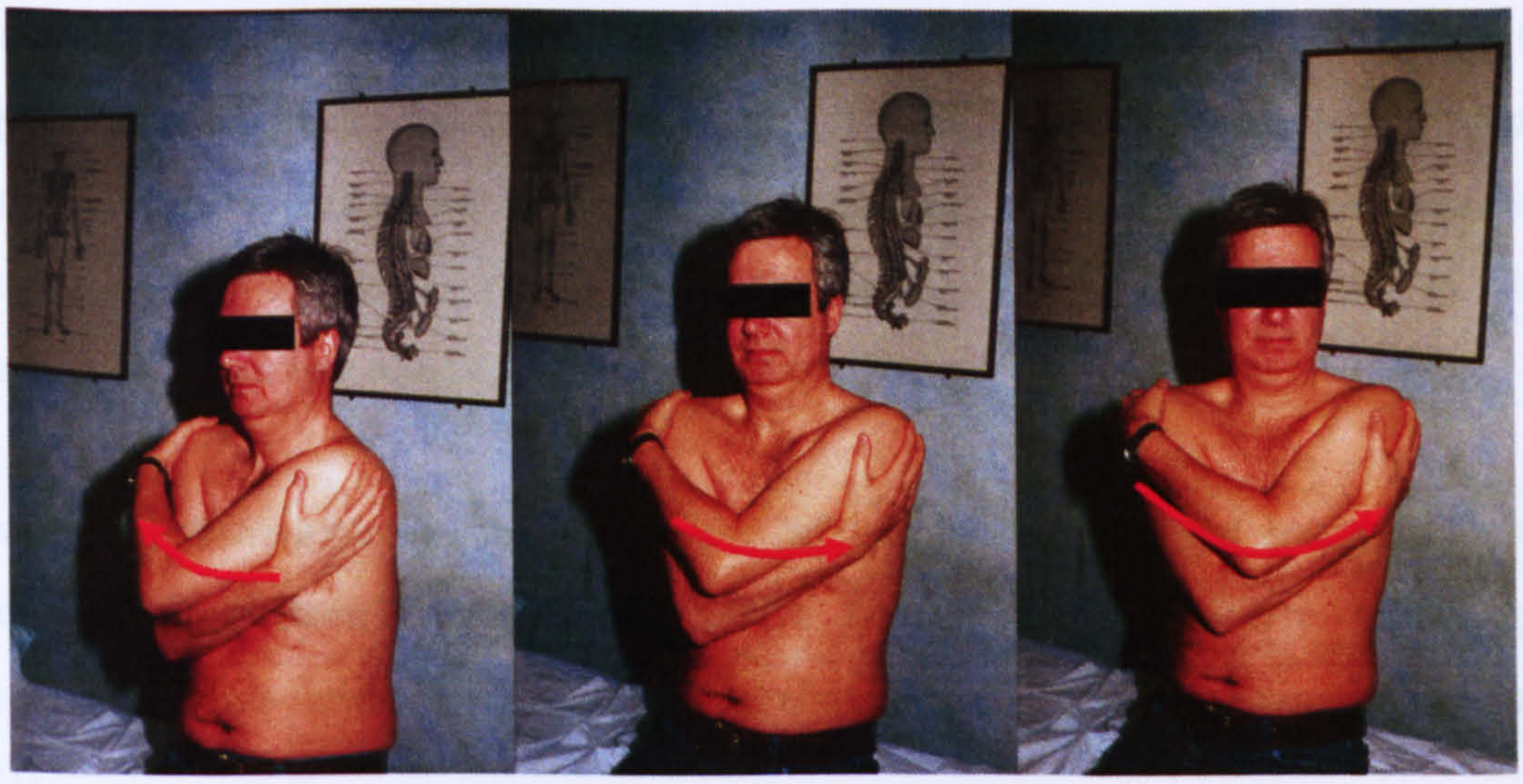


**Figure 19 Mid-thoracic rotation exercise**

The patient slowly rotates his back 5 times each way, through an arc of 45 degrees whilst sitting. When holding the shoulders, this rotation exercise gently stretches the mid thoracic spine.

With the patient remaining seated, the exercise should be repeated, again five times each way, with the arms folded at the waist. Rotating the trunk in this position improves mobility of the lower dorsal and upper lumbar segments of the spine.

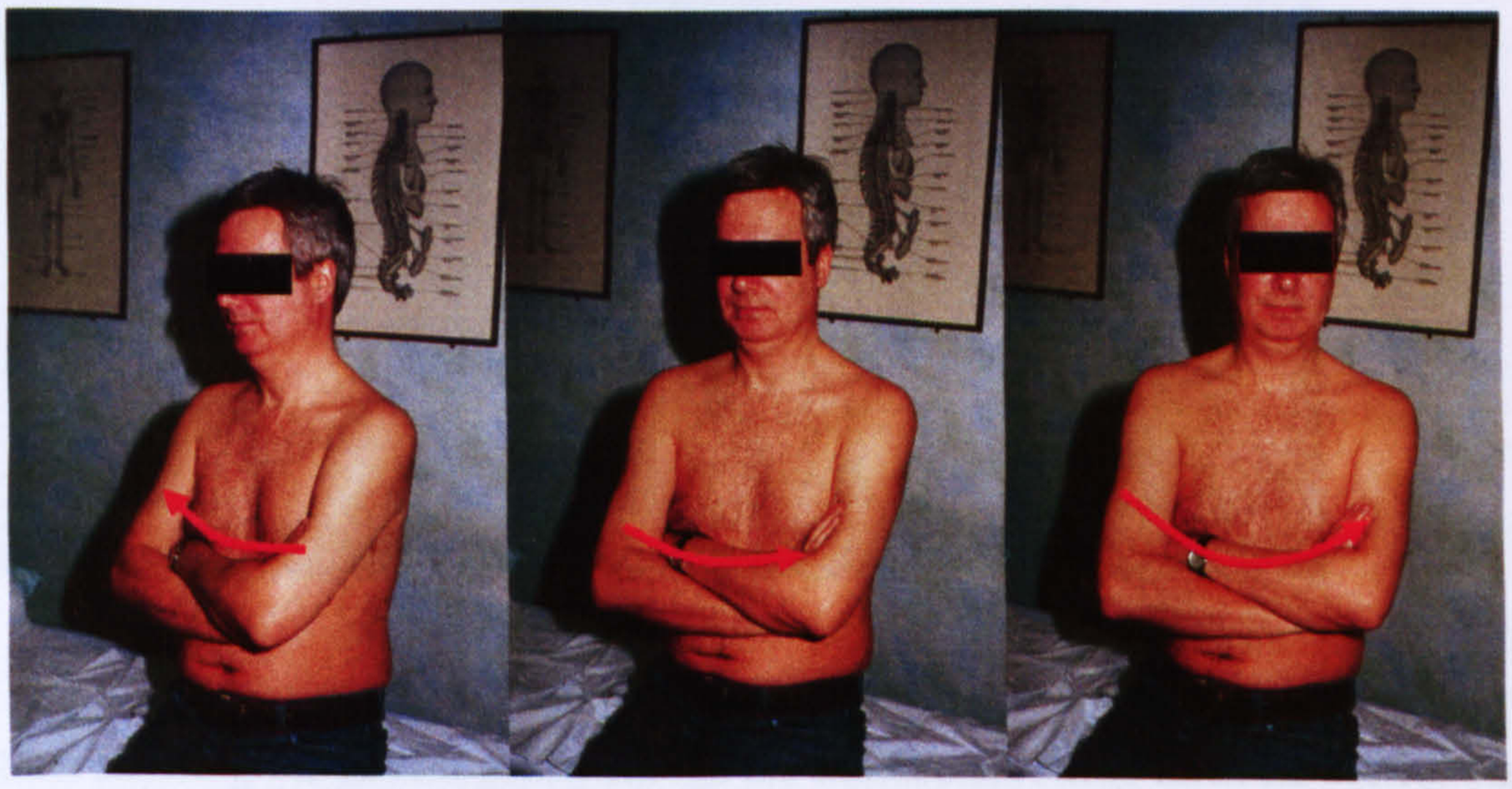


**Figure 20 Lower thoracic rotation exercise**

The patient slowly rotates his back 5 times each way, through an arc of 45 degrees whilst sitting. When folding the arms, this rotation exercise gently stretches the lower thoracic spine.

Patients were instructed to carry out the entire sequence three times a day. Since it is only a very gentle exercise, even the most severe cases of CFS/ME should not restrict the patient from doing the above exercise. However the patient was advised to cease exercises if pain developed at any time during or following the routine. The complete routine in all three positions took about one minute, if done at the correct speed.

Following the above exercise, the patient was advised to stand up, and gently shrug his/her shoulders, rolling them slowly forward five times and then slowly repeating with backwards rolls five times. This exercise was also carried out at least three times a day (see Fig. 21)

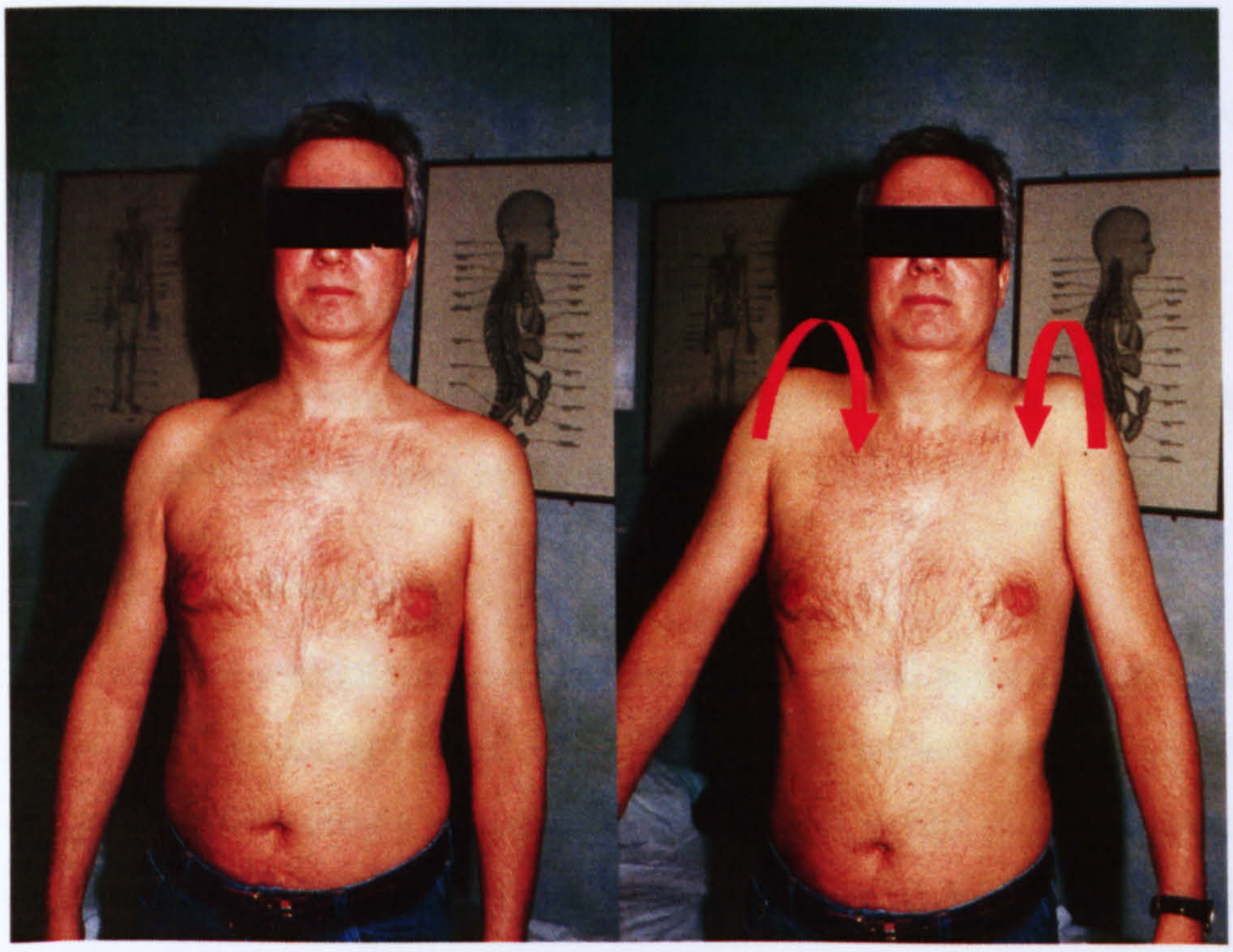


**Figure 21 Shoulder shrug exercise**

Whilst standing the patient gently shrugs his shoulders, rolling them slowly forward five times and then slowly repeating with backwards rolls five times

#### 2.2.5.2 Cross crawl

By co-ordinating activity between the right and left sides of the patient, one can stimulate both halves of the brain to work together in harmony with the whole body. This is the principal of the following exercise, known as the cross-crawl. The cross-crawl exercise is basically marching on the spot. The marching action should be slow and deliberate, with the patient's right arm moving in unison with the left leg. This action is then repeated moving the left arm forward together with the right leg. CFS/ME patients usually find this simple task difficult to perform at the beginning of therapy, since their bodies are so un-synchronised. It is very important not to move the arm and leg of the same side together, as this will only succeed in throwing the body and mind further out of balance. After practising for a while the patients were able to carry out the cross-crawl exercise without too much difficulty. The marching routine was to be done up to five minutes during an entire day, a minute or so at a time. Any exercises that over-exerted the patient were definitely to be avoided.

#### 2.2.5.3 Self massage routine

The patient was advised to aid the lymphatic drainage of the head and spine through a self massage routine developed by the author.

##### 2.2.5.3.1 Nasal release

This massage schedule begins with the patient seated applying gentle pressure to open the fronto-nasal suture and aid drainage in the sinus mucous membrane. The minimal force is accomplished by mildly pressing the pads of both second digits up against the inner canthus or conversely pulling slightly down just above the bridge of the nose. The patients choose the technique with which they feel most comfortable and which enable them to breathe easiest through the nose. During the first ten days of self treatment, the pressure referred to by the author as 'nasal release' was held for a 7 minute period. Clinically this has been shown to bring about a lasting release of the region by enhancing breathing and lymphatic drainage. After the first ten days, patients continued with 'nasal release' but only for a one minute period to maintain the improvement (see Fig. 22).

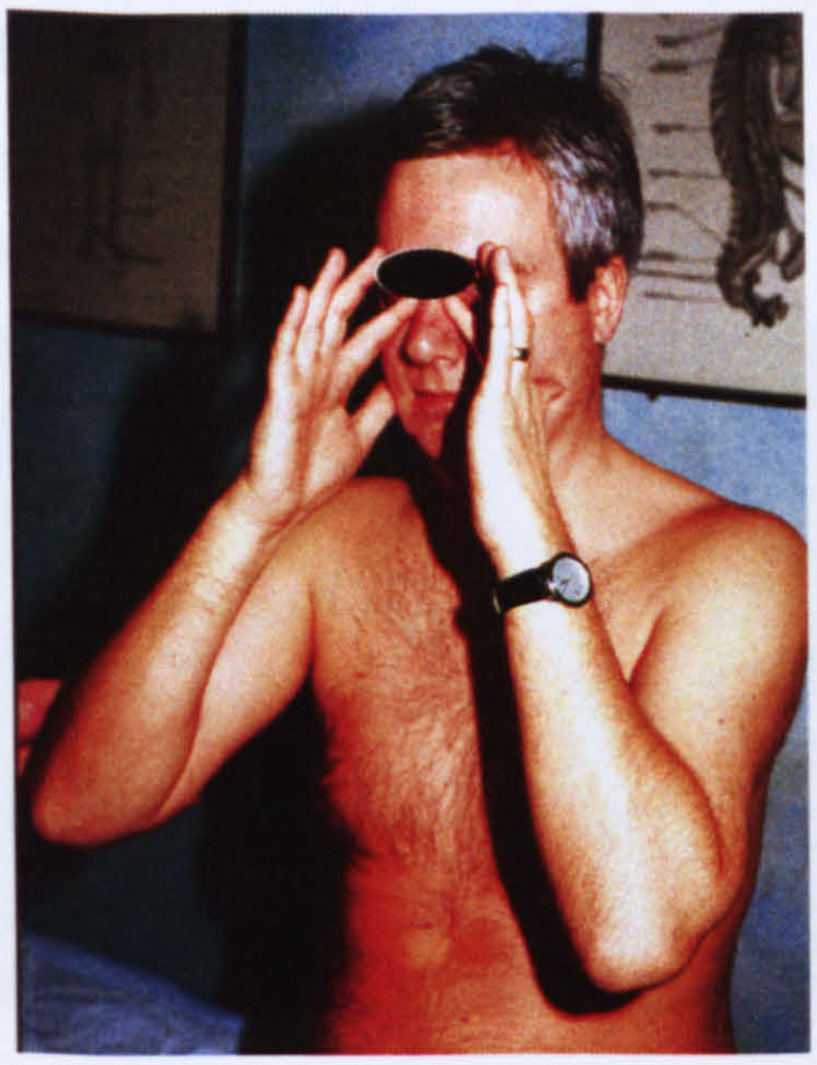


**Figure 22 Nasal release**

The seated patient gently presses the pads of both second digits up against the inner canthus or conversely pulls slightly down just above the bridge of the nose.

#### 2.2.5.3.2 Facial massage

The patients, whilst remaining seated, were then advised to gently stroke the finger-tips of one spread hand down their faces to the chin (see Fig. 23). They were instructed to carry out gentle facial effleurage for only twenty seconds with a rate of one stroke roughly every four seconds.

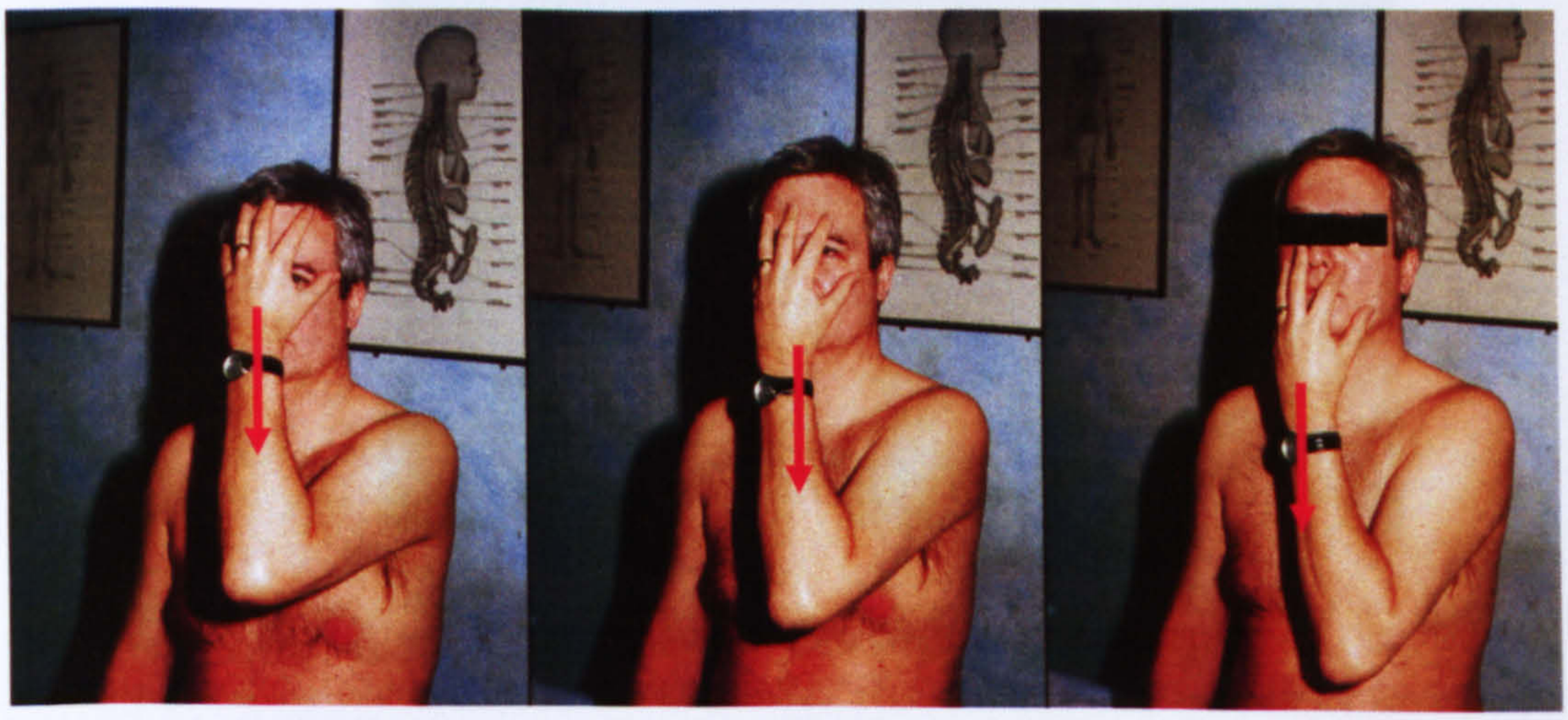


**Figure 23 Facial self massage**

The patient gently strokes the finger-tips of one spread hand down his face to the chin for twenty seconds.

#### 2.2.5.3.3 Head massage

The above gentle stroking method was then repeated for twenty seconds at a time on both sides and the back of the head down to the neck (see Fig. 24).

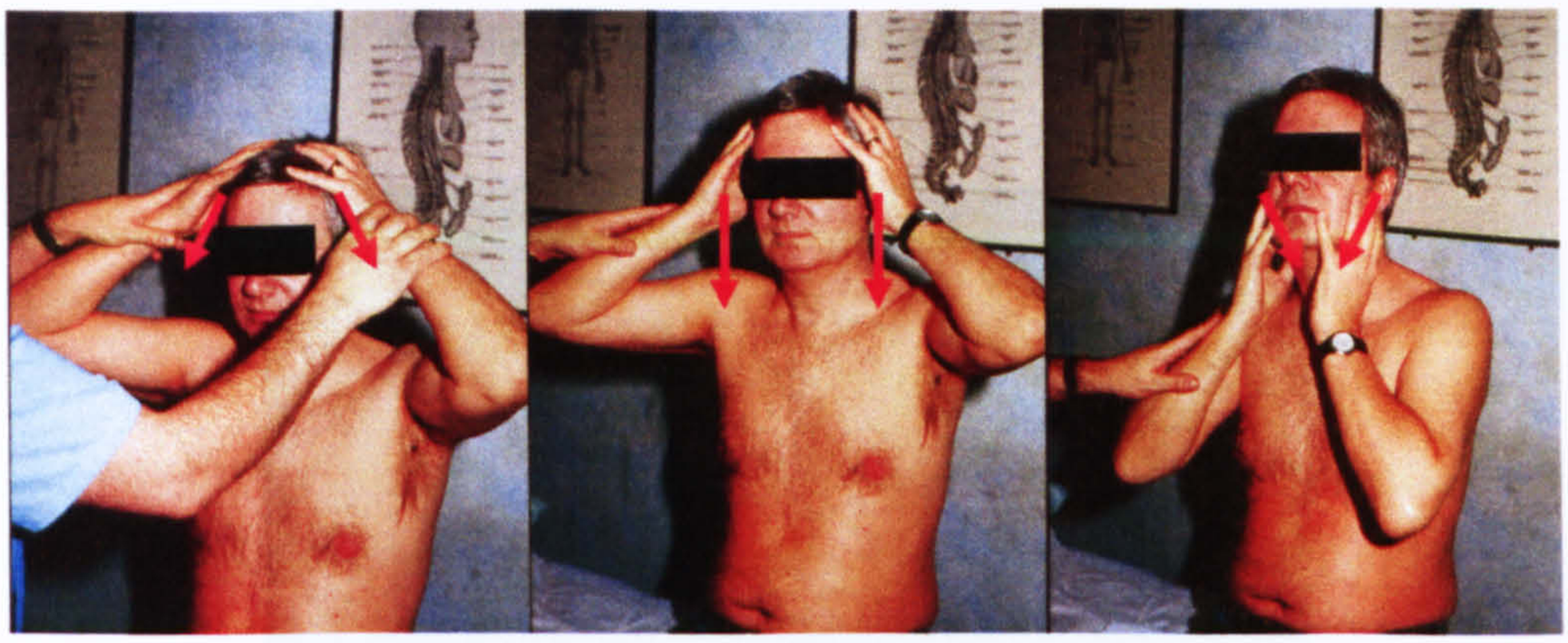


**Figure 24 Self massage to head**

The patient gently strokes the fingers of both spread hands down the sides of his head to the neck for twenty seconds.

#### 2.2.5.3.4 Anterior neck massage

The patient was then instructed to lie down and using sweet almond oil or baby oil to continue with bilateral effleurage of the neck down to the clavicles for twenty seconds each side (see Fig. 25)

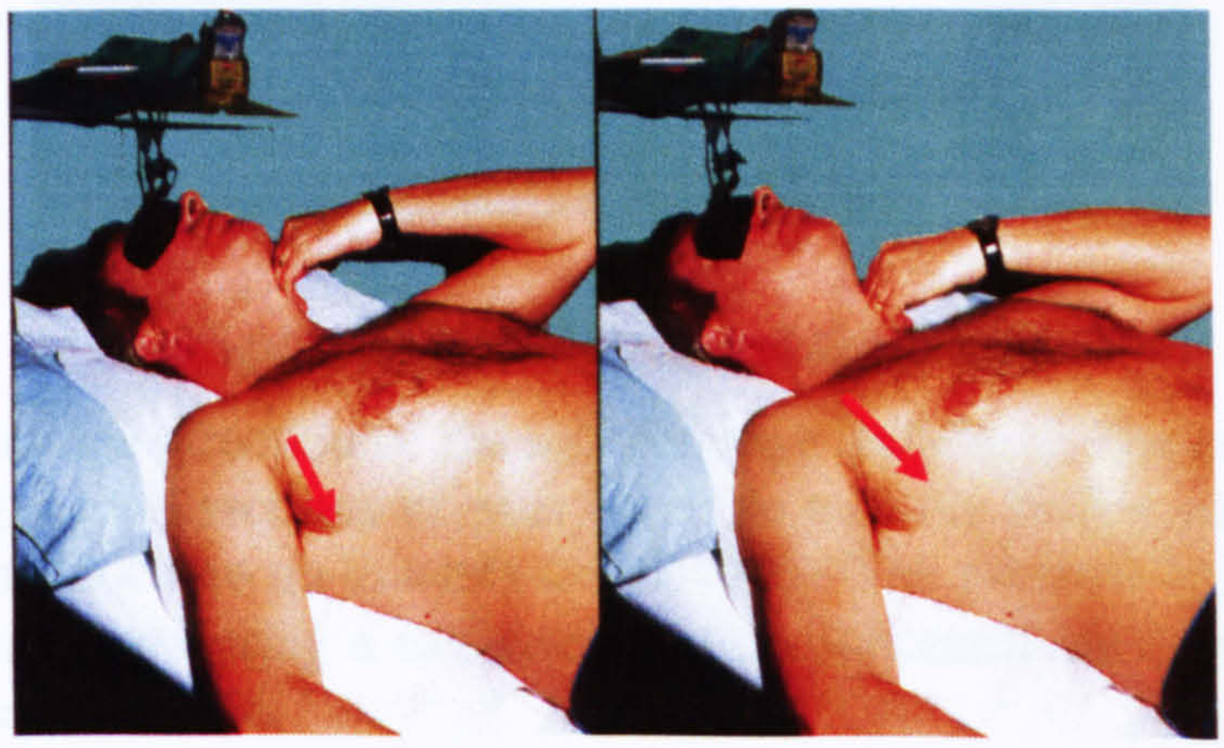


**Figure 25 Cervical self massage**

The red arrows show the direction of the self-massage technique which was always towards either clavicle on both sides for 20 secs. each side. The pressure applied by the patient should be much less than during a treatment session concentrating only on the superficial lymphatics in the self massage.

#### 2.2.5.3.5 Breast massage

The patient massaged the lateral, central and medial sections of the breast in turn for twenty seconds, with a slow rhythmic stroking manoeuvre up towards the clavicles, thus directing the lymph away from the axillary lymph nodes to avoid risk of glandular swelling (see Fig. 26).

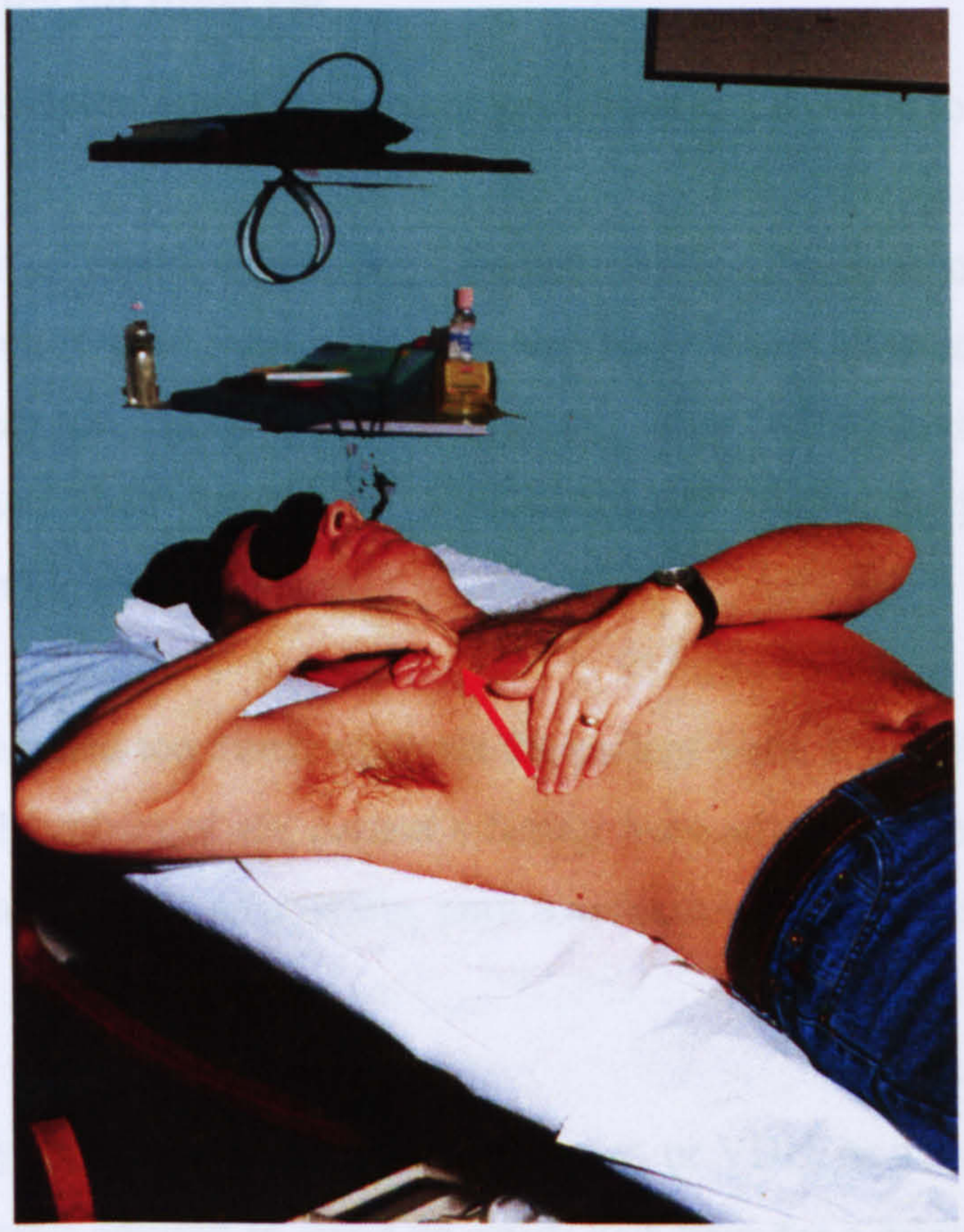


**Figure 26 Self massage of the breast**

The red arrows show the direction of the self-massage technique. The patient massages the lateral, central and medial sections of each breast in turn for twenty seconds, with a slow rhythmic stroking manoeuvre up towards the clavicles. The pressure applied by the patient should be much less than during a treatment session concentrating only on the superficial lymphatics in the self massage.

#### 2.2.5.3.6 Back massage

Having adopted a prone position, the patient received back massage from a family member or friend. The massage routine comprised of one minute of gentle upward effleurage to the sides of the spine, finishing in the shoulder region level with the clavicles. If no help was available, patients used back brushes to accomplish the back massage.

#### 2.2.5.3.7 Posterior neck massage

The self massage routine was completed with downward effleurage of the back of the neck for twenty seconds bilaterally, just in case the upward back massage was too vigorous and upward pressure was applied too high above the clavicles.

### 2.2.5.4 Advice on lifestyle

The patients were given the following general guidelines to aid return to good health.

They were advised to avoid any stress whether physical, mental or emotional where possible. No activities that exert strain on the body were allowed. If the patient's occupation involved too much physical activity, they were advised to stop work temporarily or reduce their workload. This especially applied to jobs that put extra mechanical strain on the thoracic spine.

Physical tasks that exerted too much strain on the patient were, if possible, to be done by a helpful colleague. Members of the patient's family were advised to share the workload at home, to make life as bearable as possible, until treatment had restored the sufferer to better health.

If the patient usually spent time in front of a computer, or VDU, or if they were desk-bound at work, then they were advised to stand up every half-hour for a minute or two, and walk around the office.

The patient was instructed to avoid slumping into a soft chair. When relaxing, patients were advised to lie on their side on a couch or a bed with the head well supported and a pillow between their knees. Lying on the side puts minimal strain onto the spine.

Patients were advised to strictly rotate their diet with as much diversity as possible. This reduced placing strain on any particular region of the gastro-intestinal system. Processed foods were to be avoided and brown flour and brown sugar was to replace the white variety. Stimulants such as caffeine are not healthy, particularly in CFS/ME.

Decaffeinated coffee and decaffeinated tea or herbal tea was to be drunk instead. Patients were told to eat regular, healthy meals and to drink plenty of healthy fluids such as fruit juice, or even plain mineral water. The intake of tobacco, alcohol and too much medication may exert a strain on the internal viscera, and thus the sympathetics. This will undoubtedly worsen the symptoms of CFS/ME. Therefore smoking, drinking alcohol and the taking of medication was to be kept to the minimum, and avoided if possible.

As well as the vitamin intake inherent in a healthy diet, a supplement of Vitamins C and B complex was prescribed. The former increases the patient's resistance to infection, while the latter improves general functioning of the nervous system. A high dose Vitamin C pill of 1000mg was recommended to be taken three times a week and a strong, or whole B complex tablet, to be taken once a day. Vitamins B and C are both water soluble so that any excess can be excreted from the body. However, there is a risk of developing kidney stones if the Vitamin C intake is too high, thus it is safer not to take the 1000mg pill every day (Baxmann et al., 2003).

At the beginning of treatment, the patient was treated once a week. As the symptom picture improved, there was a gradual increase in the time between the consultations.

## 2.3 Statistical methods

### 2.3.1 Symptom picture

Firstly, for each questionnaire, separate two-sample t-tests were performed on the difference of mean scores from start to months 3, 6, 9 and 12. The most important statistic after each 3 months is the p-value. Those tests with $p<0.05$ indicate significant differences between symptom reduction of the control group and the patient group at the 5% level of significance (see Appendix A9).

Secondly the estimated differences in mean reductions between the two groups were calculated, with corresponding 95% confidence intervals. These provide an alternative way of presenting the information instead of hypothesis tests. An interval that excludes zero

corresponds with a significant test. Each interval is a range of values inside which the difference in the mean score of symptom reduction (controls minus patients) lies with 95% confidence (significant if the interval excludes zero). The confidence interval also provides information about the size of the difference (note that the estimated difference lies in the middle of the interval).

Finally, for each questionnaire, a one-sample t-test was performed for patients only, to analyse any difference from month 12 until a year follow up. Ho = increase in mean score indicating a worsening of symptoms over the follow-up period.

### 2.3.2 Muscle fatigue.

The mean results of the knee extensor fatigability tests were statistically analysed using a paired t-test comparing torque X time before and after the year long study (See appendix A9).

### 2.3.3 Spinal mobility

The preliminary results of the spinal mobility tests of patients RP01 to RP07 on five test occasions at three monthly intervals were examined to see if there was any statistical significance. If there was, all the results would be examined and statistically analysed. However if these preliminary results showed no significance then, since the analysis was extremely labour intensive, it was deemed by the researchers an unnecessary excess of valuable research time and effort to continue in this line of investigation.

## 2.4 Results

### 2.4.1 Self report questionnaires

The tables and bar charts below represent the mean score obtained from all the patients for each of the questionnaires at intervals during the 12 month test period, and subsequently at a one year follow up. The score values are expressed as the mean from the group of subjects as a percentage of the maximum severity of the symptom.

### 2.4.1.1 Mean value results

In the table below (Table 4), the columns represent the mean value of each questionnaire result where 100% = the most severe case possible and 0% = symptom free.

Beneath the means are the p-values calculated using two-sample t-tests on the reductions in the scores from the start to 3, 6, 9, and 12 months respectively, comparing the mean reduction of symptoms for both groups. Those tests with $p<0.05$ indicate significant differences between the mean reductions of the control group and the patient group at the 5% level of significance. Thus if $p>0.05$ then it would signify that there was no statistical difference between the mean improvement of the patient group (1) and the control group (2). A p-value of $<0.05$ in all the questionnaires would show a significant improvement in the overall health of the patient group compared to that of the control.

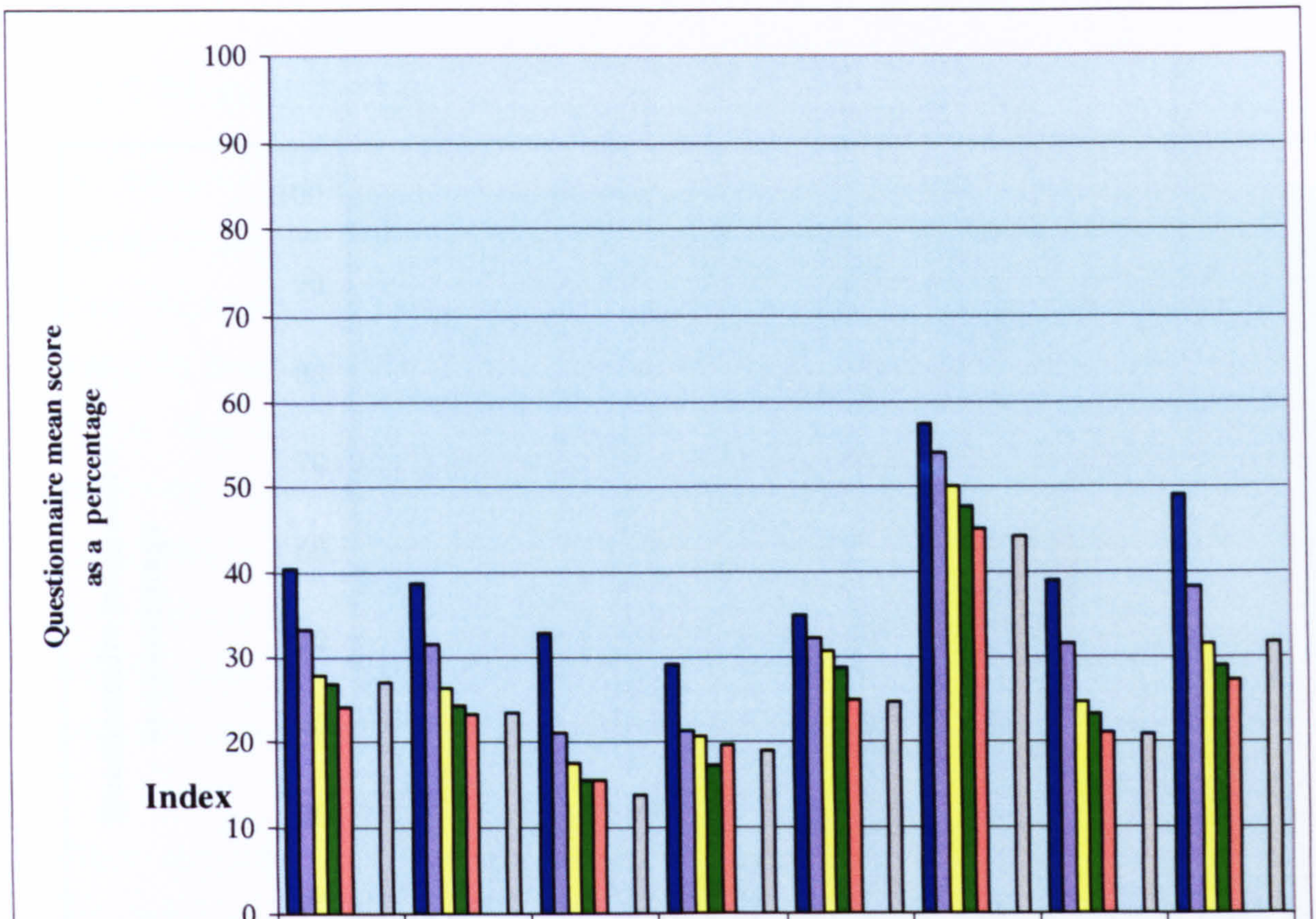
Note that the final row of Table 4 only pertains to the patient group, and shows the mean scores in the follow up a year after the end of the trial. The p-values in this row were calculated using a one-sample t-test. The scores at the end of the follow-up year were compared with the scores at 12 months. If there is no significant deterioration in the health of the patient group the p-values will all exceed 0.05.

The results are further illustrated graphically in the two bar charts Figs. 27 and 28. A reduction of symptoms is represented by a diminution of the height of the corresponding bar.

| | health % | back-pain % | Bdi % | Bai % | sleep % | cfq % | Nott % | Pfrs % |
|---|---|---|---|---|---|---|---|---|
| **Start** | | | | | | | | |
| **Group 1** | 40.58 | 38.64 | 32.87 | 29.26 | 34.96 | 57.40 | 38.9 | 48.90 |
| **Group 2** | 33.92 | 26.97 | 25.44 | 24.80 | 42.68 | 61.40 | 31.1 | 44.95 |
| **3 months** | | | | | | | | |
| **1.** | 33.28 | 31.59 | 20.99 | 21.31 | 32.23 | 53.9 | 31.56 | 38.32 |
| **2.** | 31.49 | 27.11 | 24.49 | 25.28 | 40.75 | 58.60 | 34.98 | 42.78 |
| **p-value** | 0.180 | 0.151 | 0.023 | 0.023 | 0.706 | 0.853 | 0.122 | 0.032 |
| **6 months** | | | | | | | | |
| **1.** | 27.9 | 26.41 | 17.33 | 20.61 | 30.65 | 50.00 | 24.72 | 31.56 |
| **2.** | 34.05 | 28.36 | 21.31 | 28.46 | 40.18 | 61.5 | 37.35 | 44.80 |
| **p-value** | 0.002 | 0.005 | 0.033 | 0.001 | 0.535 | 0.004 | 0.001 | 0.000 |
| **9 months** | | | | | | | | |
| **1.** | 26.88 | 24.19 | 15.26 | 17.01 | 28.83 | 47.70 | 23.14 | 29.05 |
| **2.** | 33.66 | 28.36 | 20.99 | 25.76 | 46.08 | 60.20 | 37.08 | 44.10 |
| **p-value** | 0.000 | 0.000 | 0.003 | 0.000 | 0.005 | 0.002 | 0.000 | 0.000 |
| **12 months** | | | | | | | | |
| **1.** | 23.94 | 23.07 | 15.26 | 19.40 | 24.97 | 45.00 | 21.04 | 27.34 |
| **2.** | 36.22 | 29.19 | 22.66 | 27.51 | 41.54 | 61.70 | 39.45 | 47.43 |
| **p-value** | 0.000 | 0.000 | 0.000 | 0.000 | 0.006 | 0.000 | 0.000 | 0.000 |
| **Follow up (Group 1 only)** | 27.01 | 23.35 | 13.67 | 8.92 | 24.74 | 44.2 | 20.78 | 31.9 |
| **p-value** | 0.678 | 0.529 | 0.298 | 0.069 | 0.850 | 0.837 | 0.545 | 0.194 |

**Table 6 Phase 1: Means for symptom severity showing statistical significance**

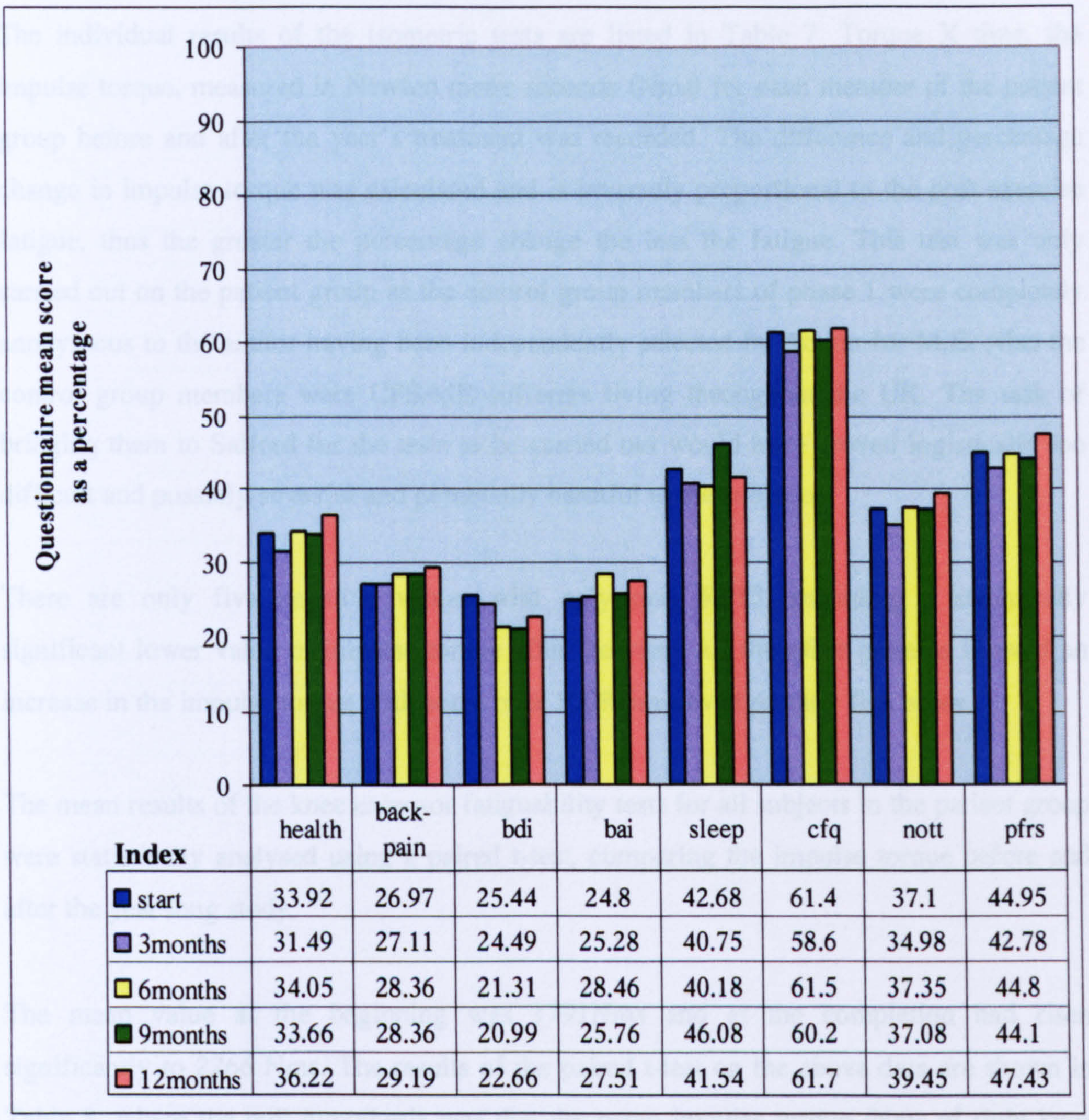
The columns represent the mean value of each questionnaire result where 100% = the most severe case possible and 0% = symptom free. The p-values were calculated using two-sample t-tests on the reductions in the scores from the start to 3, 6, 9, and 12 months respectively, comparing the mean percentage change in both groups. The p-values in the final row were calculated using a one-sample t-test, comparing the final scores with those at the end of the follow-up year.




| | health | back-pain | bdi | bai | sleep | cfq | nott | pfrs |
|---|---|---|---|---|---|---|---|---|
| start | 40.58 | 38.64 | 32.87 | 29.26 | 34.96 | 57.4 | 38.9 | 48.9 |
| 3months | 33.28 | 31.59 | 20.99 | 21.31 | 32.23 | 53.9 | 31.56 | 38.32 |
| 6months | 27.9 | 26.41 | 17.33 | 20.61 | 30.65 | 50 | 24.72 | 31.56 |
| 9months | 26.88 | 24.19 | 15.26 | 17.01 | 28.83 | 47.7 | 23.14 | 29.05 |
| 12months | 23.94 | 23.07 | 15.26 | 19.4 | 24.97 | 45 | 21.04 | 27.34 |
| | | | | | | | | |
| | | | | | | | | |
| follow up | 27.01 | 23.35 | 13.67 | 18.92 | 24.74 | 44.2 | 20.78 | 31.9 |

**Figure 27 Bar chart of patient group's mean scores (phase 1)**

The bar chart shows the changes in the questionnaire scores in the treated group over the course of the first clinical trial and the year follow-up. The questionnaires were as follows: Column 1. Health = A general health questionnaire examining most common symptoms of CFS/ME; Column 2. examined back pain; Column 3. bdi = The revised Beck depression inventory; Column 4. bai = The Beck anxiety inventory; Column 5 = The Morgan-Gledhill sleep questionnaire; Column cfq = Broadbent's cognitive function questionnaire; Column 7. = The Nottingham Health Questionnaire which concentrates on symptoms of fatigue; Column 8. pfrs= The Profile of Fatigue Related States. As all the questionnaires have different scales and scoring systems, the results were converted to a percentage of the maximum score possible.




| Index | health | back-pain | bdi | bai | sleep | cfq | nott | pfrs |
|---|---|---|---|---|---|---|---|---|
| start | 33.92 | 26.97 | 25.44 | 24.8 | 42.68 | 61.4 | 37.1 | 44.95 |
| 3months | 31.49 | 27.11 | 24.49 | 25.28 | 40.75 | 58.6 | 34.98 | 42.78 |
| 6months | 34.05 | 28.36 | 21.31 | 28.46 | 40.18 | 61.5 | 37.35 | 44.8 |
| 9months | 33.66 | 28.36 | 20.99 | 25.76 | 46.08 | 60.2 | 37.08 | 44.1 |
| 12months | 36.22 | 29.19 | 22.66 | 27.51 | 41.54 | 61.7 | 39.45 | 47.43 |

**Figure 28 Bar chart of control group's mean scores (Phase 1)**

The bar chart shows the changes in the questionnaire scores in the untreated control group over the course of the first clinical trial. As in Fig. 27 the results were converted to a percentage of the maximum score possible for each questionnaire.

## 2.4.2 Muscle fatigue

The individual results of the isometric tests are listed in Table 7. Torque X time, the impulse torque, measured in Newton metre seconds (Nms) for each member of the patient group before and after the year's treatment was recorded. The difference and percentage change in impulse torque was calculated and is inversely proportional to the post exercise fatigue, thus the greater the percentage change the less the fatigue. This test was only carried out on the patient group as the control group members of phase 1 were completely anonymous to the author having been independently selected by Action for M.E. Also the control group members were CFS/ME sufferers living throughout the UK. The task of bringing them to Salford for the tests to be carried out would have proved logistically too difficult and possibly stressful and potentially harmful to the subjects.

There are only five negative values with only one, RP13, recording a statistically significant lower value of impulse torque after the year. All the other patients showed an increase in the impulse torque with some over 100% improved on their first score.

The mean results of the knee extensor fatiguability tests for all subjects in the patient group were statistically analysed using a paired t-test, comparing the impulse torque before and after the year long study.

The mean value at the beginning was 1791Nms and at the completion had risen significantly to 2266 Nms. The results of the paired t-test on the above data are shown in Table 8, where the null hypothesis was that the mean impulse torque /Nms of right knee during first 30 seconds of final push was the same for tests 1 and 2.

| | | Test 1 | Test 2 | | Difference | | Percentage |
|---|---|---|---|---|---|---|---|
| Patient | | (year start) | ( year end) | | Between | | Change |
| code no. | | /Nms | Nms | | Test 1 & 2/Nms | | % |
| RP01 | | 606 | 2211 | | 1605 | | 264.85 |
| RP02 | | 1077 | 1767 | | 690 | | 64.07 |
| RP03 | | 512 | 1255 | | 743 | | 145.12 |
| RP04 | | 716 | 1783 | | 1067 | | 149.02 |
| RP05 | | 732 | 1182 | | 450 | | 61.48 |
| RP06 | | 1264 | 1559 | | 295 | | 23.34 |
| RP07 | | 1982 | 2641 | | 659 | | 33.25 |
| RP11 | | 583 | 711 | | 128 | | 21.96 |
| RP12 | | 1691 | 2971 | | 1280 | | 75.69 |
| RP13 | | 1917 | 1366 | | -551 | | -28.74 |
| RP14 | | 5033 | 5014 | | -19 | | -0.38 |
| RP15 | | 2484 | 2945 | | 461 | | 18.55 |
| RP16 | | 2653 | 2990 | | 337 | | 12.7 |
| RP17 | | 1807 | 2604 | | 797 | | 44.11 |
| RP19 | | 245 | 704 | | 459 | | 187.35 |
| RP20 | | 518 | 826 | | 308 | | 59.46 |
| RP21 | | 659 | 1331 | | 672 | | 101.97 |
| RP23 | | 4776 | 4670 | | -106 | | -2.22 |
| RP24 | | 475 | 1179 | | 704 | | 148.21 |
| RP25 | | 1440 | 1777 | | 337 | | 23.4 |
| RP26 | | 5140 | 4658 | | -482 | | -9.38 |
| RP27 | | 277 | 1343 | | 1066 | | 384.84 |
| RP28 | | 1793 | 2118 | | 325 | | 18.13 |
| RP29 | | 1109 | 1320 | | 211 | | 19.03 |
| RP30 | | 1594 | 1866 | | 272 | | 17.06 |
| RP31 | | 700 | 863 | | 163 | | 23.29 |
| RP32 | | 1695 | 3221 | | 1526 | | 90.03 |
| RP33 | | 3002 | 2927 | | -75 | | -2.5 |
| RP34 | | 3698 | 3742 | | 44 | | 1.19 |
| RP35 | | 1727 | 2658 | | 931 | | 53.91 |
| RP36 | | 2757 | 3476 | | 719 | | 26.08 |
| RP38 | | 1364 | 1998 | | 634 | | 46.48 |
| RP40 | | 3093 | 3103 | | 10 | | 0.32 |
| | | | | | | | |
| MEAN | | 1791.48 | 2266.03 | | 474.55 | | 26.49 |

**Table 7 Phase 1: Impulse torque /Nms of right knee during first 30 seconds of final push**

Column 3 = impulse torque at the start of the research. Column 4 = impulse torque at the end of the year. Column 6 = column 4 - 3. The final column shows the percentage change in the impulse torque. A minus sign indicates a reduction in the impulse torque.

| | Number of subjects | Mean Impulse Torque/ Nms | Standard Deviation |
|---|---|---|---|
| Test 1 | 33 | 1791 | 1,353 |
| Test 2 | 33 | 2266 | 1,170 |
| | | Mean Difference = 475 | % Mean Difference 26.49 |

**Table 8 Mean difference of impulse torque in patient group (phase 1)**

The table shows the mean difference in impulse torque, pre and post treatment over a year, calculated from the results in Table 7.

Estimated difference in means μ2- μ1 is 474.5 with 95% confidence interval (296.4, 652.7). μ1 = μ2 has a two-sided test statistic of 5.43 on 32 degrees of freedom, resulting in a p-value of 0.000 to three decimal places. Hence, the null hypothesis H0 was rejected at the 5% (even at the 0.1%) level demonstrating that the means are significantly different.

## 2.4.3 Spinal mobility

The preliminary results of spinal mobility tests of patients RP01 to RP07 on five occasions at three monthly intervals are listed below in Table 9 measuring the angle CTL at probe position T in the mid thoracic spine (see Appendix A8). The percentage changes both periodically, every three months (table 10), and relative to the start of treatment (table 11), have been recorded. The mobility tests were meant to be carried out every 3 months although due to damaged equipment many missed out on the examination at 9 months, thus the % change in patients RP04-07 could not be calculated from 6-9 months and 9-12 months.

The mean values in both charts clearly demonstrate that the thoracic mobility of these patients varied very little from the beginning to the conclusion of Phase 1. It was also noted

that there was no correlation with the amount of mobility and improvement of CFS/ME symptoms, the significance of which is discussed at length in section 2.5.3.

As was the case with the tests on muscle fatiguability, the spinal mobility investigation was only carried out on the patient group to avoid compromising the anonymity and health of the control group members of phase 1.

| | Start<br>O | 3 months | 6 months | 9 months | End<br>12 months |
|---|---|---|---|---|---|
| RP01 | 150.19 | 150.30 | 152.51 | 154.42 | 144.06 |
| RP02 | 139.27 | 151.10 | 144.76 | 146.65 | 146.07 |
| RP03 | 138.04 | 144.04 | 140.05 | 138.86 | 140.13 |
| RP04 | 149.60 | 145.41 | 151.42 | ***** | 150.97 |
| RP05 | 138.87 | 134.99 | 133.14 | ***** | 133.57 |
| RP06 | 139.43 | 136.62 | 138.94 | ***** | 137.17 |
| RP07 | 137.74 | 137.67 | 135.00 | ***** | 135.45 |

**Table 9 Chart showing angular values of mobility in thoracic spine of patients RP01-7**

The table shows the angular values of probes CTL for flexion of the mid thoracic spine in 7 of the patients treated with the chosen osteopathic method in phase 1 of the study. The angles were calculated using the Salford biomechanics workstation which digitised the video footage of the patients bending in full flexion (see Appendix A8).

| | % change | | % change | | % change | | % change |
|---|---|---|---|---|---|---|---|
| | 0-3 months | | 3-6 months | | 6-9 months | | 9-12 months |
| RP01 | 0.07 | | 1.47 | | 1.25 | | -6.71 |
| RP02 | 8.49 | | -4.2 | | 1.31 | | -0.4 |
| RP03 | 4.35 | | -2.77 | | -0.85 | | 0.91 |
| RP04 | -2.8 | | 4.13 | | ***** | | ***** |
| RP05 | -2.79 | | -1.37 | | ***** | | ***** |
| RP06 | -2.02 | | 1.7 | | ***** | | ***** |
| RP07 | -0.05 | | -1.94 | | ***** | | ***** |
| | | | | | | | |
| Mean | 0.75 | | -0.42 | | 0.57 | | -2.06 |

**Table 10 Chart showing periodic % change in angular values of mobility in thoracic spine of patients RP01-7**

The table examines the percentage change in CTL angular value of full flexion in the mid-thoracic spine, point T, in the first 7 patients at each 3 monthly stage compared with the previous stage. The mobility tests were meant to be carried out every 3 months although due to damaged equipment many missed out on the examination at 9 months, thus the % change in patients RP04-07 could not be calculated from 6-9 months and 9-12 months.

| | % change | | % change | | % change | | % change |
|---|---|---|---|---|---|---|---|
| | 0- 3 months | | 0-6 months | | 0-9 months | | 0-12 months |
| RP01 | 0.07 | | 1.54 | | 2.82 | | -4.08 |
| RP02 | 8.49 | | 3.94 | | 5.3 | | 4.88 |
| RP03 | 4.35 | | 1.46 | | 0.59 | | 1.51 |
| RP04 | -2.8 | | 1.22 | | ***** | | 0.92 |
| RP05 | -2.79 | | -4.13 | | ***** | | -3.82 |
| RP06 | -2.02 | | -0.35 | | ***** | | -1.62 |
| RP07 | -0.05 | | -1.99 | | ***** | | -1.66 |
| | | | | | | | |
| Mean | 0.75 | | 0.24 | | 2.9 | | -0.55 |

**Table 11 Chart showing % change from start in angular values of mobility in thoracic spine of patients RP01-7**

The table examines the percentage change in CTL angular value of full flexion in the mid-thoracic spine, point T, in the first 7 patients at each 3 monthly stage compared with the value at the start of the study. As mentioned above damaged equipment caused many of the subjects to miss out on the examination at 9 months, thus the % change in patients RP04-07 could not be calculated from 0-9 months.

The digital analysis of the video footage was extremely labour intensive and time consuming, thus as there was no correlation in the first group of patients, without even showing a trend of increased angular movement, the digital analysis of spinal movements was discontinued.

## 2.5 Discussion

### 2.5.1 Questionnaire results

Some results require a more detailed analysis and explanation. It was postulated that pain in the neck and back of the CFS/ME subjects is likely related to a mechanical dysfunction. Osteopathic practitioners would expect this pain to be relieved by manual treatment of this region. The questionnaire relating to back pain (Questionnaire 2) produced the anticipated result, considering the control group were not able to receive manual treatment for the duration of their involvement in the project and supported the original postulation as shown in Table 4, column 2. Note that when the standard treatment ceased for most subjects in the patient group during the year follow-up, the back pain scores worsened. Four members of the patient group chose to continue treatment with the author as private fee-paying patients during the follow up year

The Beck Depression Inventory (Questionnaire 3) produced an interesting result as shown in Table 4, column 3. These scores clearly demonstrate that the depression level of the control was steadily decreasing during the first 9 months. This may be due to the antidepressants taken by some of the control subjects. This particular result differs from most of the other symptoms of the control group, all of which deteriorated with time. This corroborates the claim that CFS/ME is not a depressive disorder otherwise we would have expected to show some improvement in the other symptoms as the depression levels dropped.

The results of the final questionnaire No. 8 (The Profile of Fatigue Related States) see Table 4, column 8, are particularly important as this was the only established and tested questionnaire developed specifically for the symptoms associated with CFS/ME (Ray,

1992). The overall improvement in the PFRS scores of the patient group from a mean score of symptom severity of 48.9% down to 27.34% compared with the control group's score increasing in symptom severity of 44.95% up to 47.43%, adequately demonstrates the validity of the treatment programme.

In the follow up study (see Appendix A9, p297) the p-value in all questionnaire results exceeded 0.05, demonstrating that the treatment effects were long-lasting with most of the patients discontinuing treatment following the initial year's study with insignificant change in symptom picture.

## 2.5.2 Muscle fatigue

The tests involving measurement of impulse torque by the quadriceps muscle also clearly demonstrated that the treatment had caused a change for the better. A previous study on patients with CFS/ME (Wong *et al.*, 1992) has demonstrated that the reduced capacity for dynamic exercise is also associated with reaching exhaustion much more rapidly than normal subjects, at which point these patients have relatively reduced intracellular concentrations of ATP. The study concluded that there was a defect in oxidative metabolism with a resultant acceleration of glycolysis in the working skeletal muscles of a CFS/ME sufferer. Impaired blood flow is a possible explanation for a reduced oxygen supply to the muscle resulting in the above finding. However, at the end of this stage it was felt more research had to be conducted to understand the nature of the fatigue and to investigate the reason for the improvement following the chosen osteopathic treatment.

## 2.5.3 Spinal mobility

As mentioned earlier Korr (1979) proposed that spinal dysfunction would lead to disturbances in the muscular fatigability, sensory excitability, immunological mechanisms and endocrine functions due to an impairment in normal sympathetic efferent flow If Korr's (1979) findings were correct then Spinal mobility in the present study would be expected to improve as the severity of the symptoms lessened.

The present results of the spinal mobility test (Tables. 9, 10 and 11) suggest that there is little correlation between thoracic spinal movement and the symptoms of the patients. The effects of the treatment could be analogous to lubricating a rusty door hinge. The result will be a door that opens and closes smoothly and quietly but the range of movement is limited to the arc between the doorpost and the adjoining wall. In other words, by relaxation of surrounding soft tissue with less spinal and paraspinal discomfort, the treatment improves the quality of movement of the spine but not quantity.

Clinical findings argue strongly for a biomechanical and/or drainage component (See section 5.2). The precise nature of the processes that produce the significant improvement given by osteopathic treatment was an important question that remained unanswered following Phase 1 of this study. In relation to this a common clinical feature observed in the patients was a reduction in the quality of movement of the upper spine with evidence of long term mechanical dysfunction. The latter often appeared to be associated with the patient's past history (e.g. work, accident or physical exertion related upper spine involvement). In turn there was a strong indication that the osteopathic manipulation and relaxation of soft tissue improved circulation of blood, cerebrospinal fluid and lymph in the cranial and upper spinal regions of the patients. The following two cardinal features of the CFS/ME patients were palpated using standard osteopathic manual proprioceptive and palpatory techniques:

1. A significant reduction of mobility in the cranio-sacral rhythm / involuntary mechanism.

2. Congestion of the cervical and thoracic lymph vessels especially in the breasts and in most cases significantly more in the left side than the right.

In relation to the latter it is thought that there is drainage of approximately 75% of lymph in the breast tissue to the axillary nodes. Lymph vessels from deep tissues of the thoracic wall drain mainly to the parasternal, intercostal and diaphragmatic nodes. A plexus in the interlobular connective tissue and walls of the milk ducts communicate with the plexus around the nipple, and also with a plexus of minute vessels on adjacent deep fascia. This

pathway offers an alternative route when the usual pathway is blocked. Congested lymph vessels are apparently found in all cases of CFS/ME and this can be explained when viewing the factors aiding propulsion of lymph from tissue spaces to lymph nodes and the venous blood stream. These are as follows:

1. Filtration pressure
2. Contraction of neighbouring muscles
3. Pulsation of neighbouring arteries
4. Respiratory movements
5. Sympathetic nerve control of smooth muscle walls causing pulsatile contractions in thoracic duct aided by valves along its structure which maintain unidirectional flow (Kinmonth, 1982).

This last factor has been largely overlooked for decades and has received little attention from the medical world. However it has a potential of major significance when analysing the possible pathological process leading to CFS/ME. The afferent sympathetic outflow, in particular, may be modified by the treatments.

To further understand how the sympathetic nervous system may be involved in the pathogenesis of CFS/ME and how the improvement of sympathetic function may be responsible for some of the decline in the symptoms discussed in this section, one has to examine the control mechanisms involved. In this respect aspects of the Autonomic Nervous System (ANS) and its centre the hypothalamus are discussed.

### 2.5.3.1 The hypothalamus

The hypothalamus is approximately four cubic centimetres in size and represents 0.3% of the human brain (Williams, 1995). It has a central role in the control of the ANS and hormonal activity. Thus a dysfunctional hypothalamus can have major effects on these two important homeostatic systems which are considered separately below.

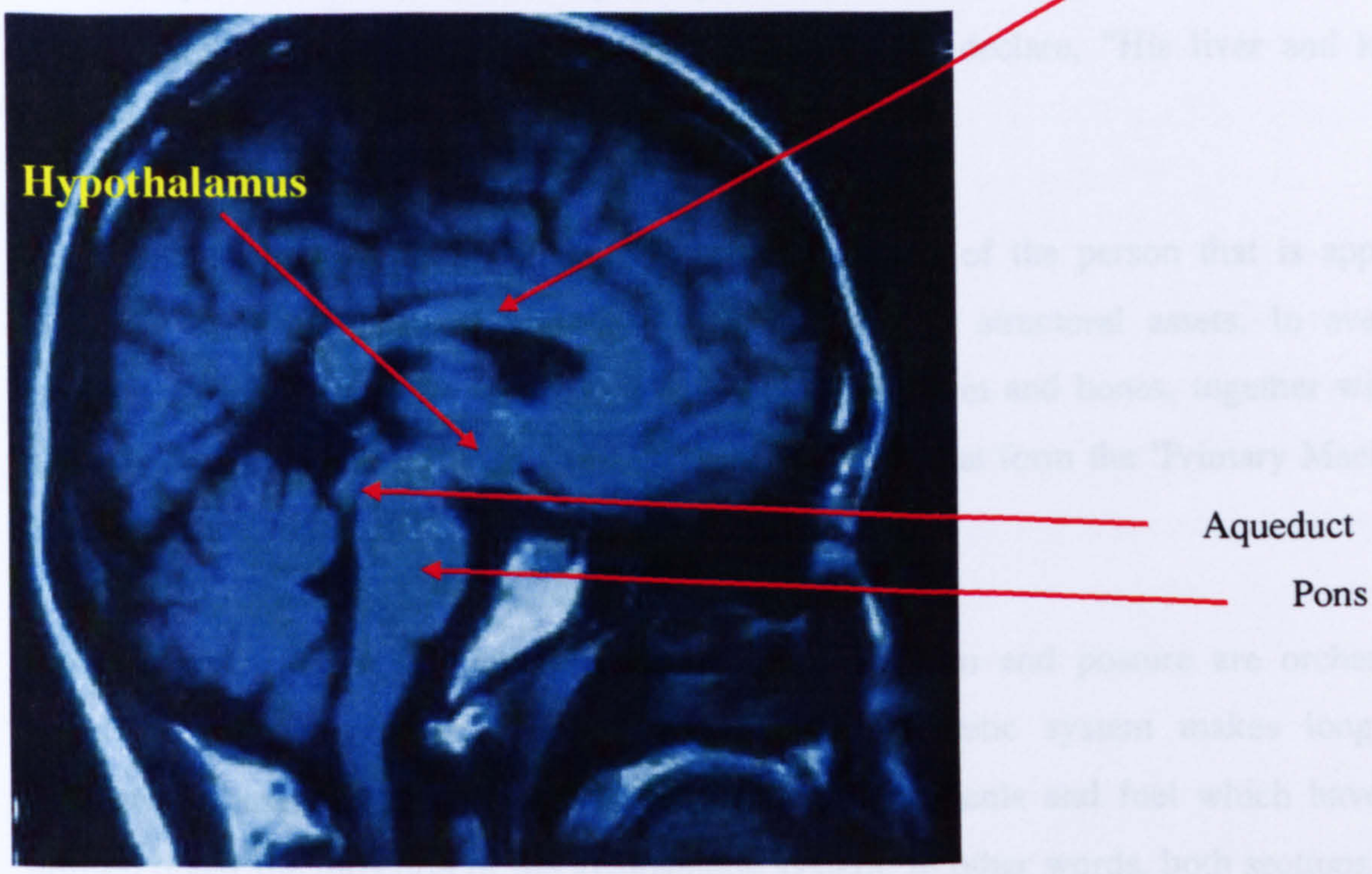



**Figure 29 Sagittal view of brain showing position of the hypothalamus**

This MR image shows just how small the hypothalamus is in relation to the entire brain. The scan also reveals the central location of the hypothalamus close to the important pons, frontal lobe, just below the limbic system and in the heart of the ventricular system.

#### 2.5.3.1.1 Autonomic activity

Whilst the overall control centre of the autonomic nerves lies in the brain, the sympathetic nervous system largely resides within the spinal cord. Along with the rest of the autonomic system, the parasympathetic and the endocrine system, they are responsible for controlling visceral, circulatory and metabolic activity. However, the performance of the sympathetic system can be greatly affected by mechanical and postural strain in the mid section of the spine, from the first thoracic vertebra to the second lumbar segment.

Osteopathic philosophy views the neuromuscular-skeletal system as the primary machinery of life, with the internal organs being secondary and supportive (Korr, 1978). It is important to understand why osteopaths view the muscles and bones as the main apparatus of the body. When a person moves, talks and breathes, the musculo-skeletal system is the structure which is directly involved. When one compliments a friend on how they look, one

doesn't say "Oh what a beautiful spleen you have!" and likewise, if one is praising the performance of an employee, a manager is unlikely to declare, "His liver and kidney certainly work well."

When one observes a fellow human, it is the make-up of the person that is apparent, including their build, shape and how they utilise their structural assets. In everyday existence, it is the muscles, tendons, ligaments, joints, skin and bones, together with the nerves supplying these structures (the Somatic Nerves), that form the 'Primary Machinery of Life' (Korr, 1978).

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 can result from inconsistency between demands of the neuromuscular-skeletal system (the Primary Machinery) and the ability of bodily systems to maintain adequate provision for normal function. 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, muscles are definitely the main consumers of the body.

The parasympathetic ganglia are mainly situated in the target organ. Their postganglionic fibres innervate all the internal organs including the eye. The uppermost fibres in the head supply the lacrimal glands of the eye which produce tears. A major parasympathetic nerve from the brain is the vagus, which supplies the organs of the neck, thorax, pelvis and genitalia.

The sympathetic postganglionic fibres supply all the organs innervated by the parasympathetic nerves, although the distribution to different parts of the organ may vary. The blood supply to the body is almost entirely under the control of the sympathetic

nervous system, except the vasculature of the pelvic organs and genitalia which are under parasympathetic regulation. A disturbance of sympathetic control over the peripheral circulation including the muscles may be part of the cause of the muscular symptoms in CFS/ME. This phenomenon was explored in phase 2 of the research.

It should be noted that the reduced fatigability of the quadriceps was not achieved by any direct treatment on the lower extremity, or by any exercise regime to improve muscle strength in the legs. The author's treatment programme was based solely on the hypothesis that by using manual techniques to reduce disturbed afferent sympathetic impulses, the overall sympathetic nervous system eventually begins to function normally, thus improving visceral function and the circulation in body tissues, including skeletal muscle.

Sympathetic influence over arterial pressure and peripheral blood resistance affects the cardiac output, as well as many other metabolic processes. The parasympathetic vagus nerve modifies the rhythm of the heart, but the sympathetic nerves regulate the entire cardiovascular system, in accordance with what is going on in the body as a whole.

The sympathetic nervous system differs from the parasympathetic in the following four ways:

1. The parasympathetic nerve supply is almost entirely visceral, exerting most of its control over the internal organs. The sympathetic nerves, however, regulate functioning of the skin, bones, ligaments, tendons and parts of the somatic nervous system, plus the skeletal muscle as well as the organs.
2. The parasympathetic nerves are more specific, with individual nerves supplying a specific target organ. The sympathetic effects are more widespread due to a fanning out of the nerves to all tissues.
3. The parasympathetic nerves control blood supply only to the genitalia. The sympathetic nerves control the circulation throughout the rest of the body.
4. The parasympathetic system is not directly affected by the requirements of the body, but the sympathetic nerves are influenced and controlled by the demand of other bodily systems (See Fig. 30).

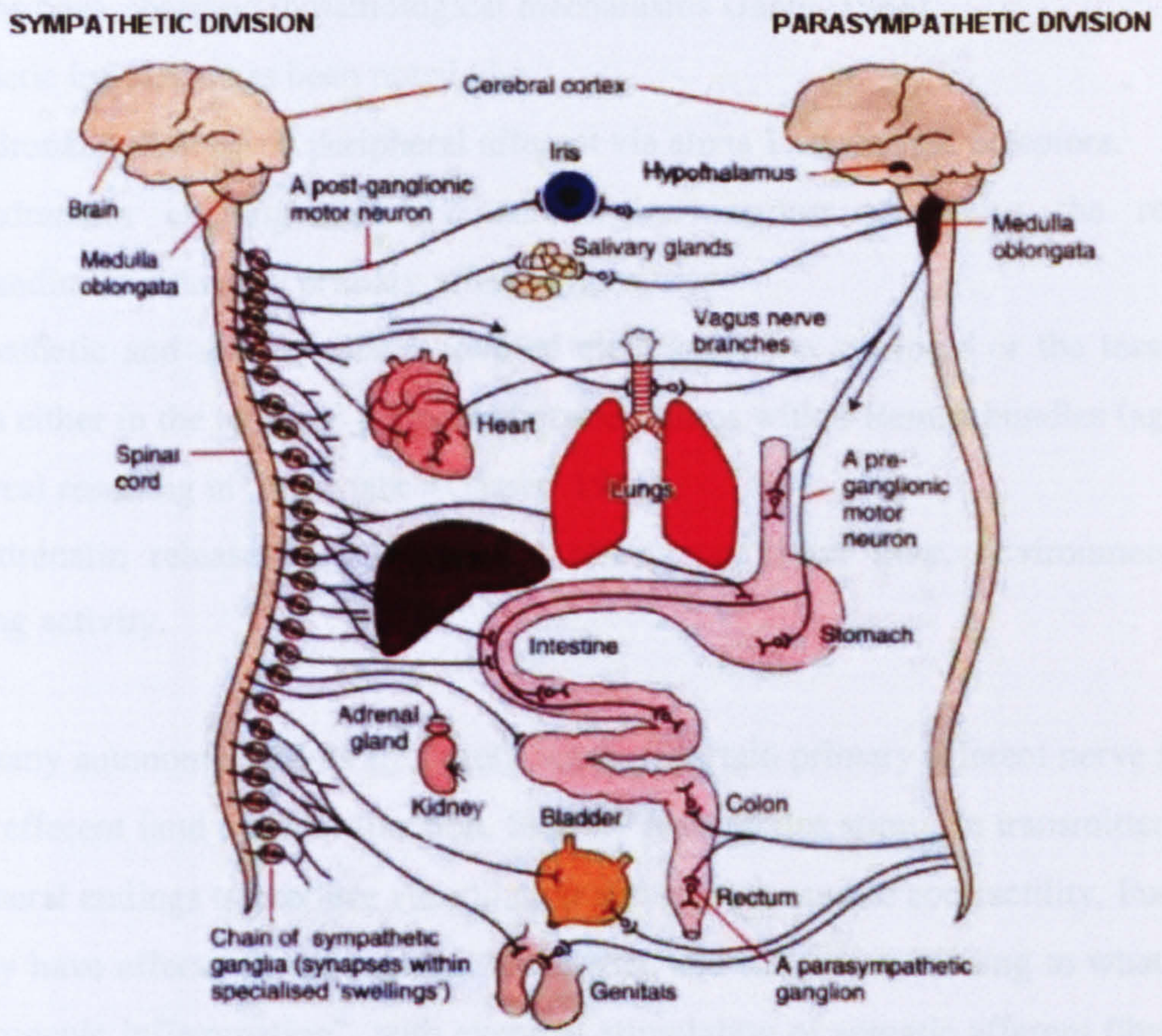



**Figure 30 The efferent (motor) component of the autonomic nervous system**

Waugh H, Mahon M. 2001,

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Since the sympathetic ganglia are centrally located, post-ganglionic sympathetic efferents can spread out exerting their influence systemically, unlike the parasympathetic ganglia located at the target organ.

Anatomically the somatic motor nerves, which stimulate skeletal muscle contraction, 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 muscles. Sympathetic nerves, due to their close proximity to motor nerves, are also equally sensitive to stimuli from sensory inputs, higher centres or interspinal nerves. Also, since spinal nerve roots contain both somatic and sympathetic fibres, both are vulnerable to mechanical trauma.

The connection between peripheral somatic nociceptive afferent fibres and sympathetic nerves has been observed in pathological mechanisms (Janig, 1988).

Sympathetic influence has been noted via:

1. Noradrenalin directly on peripheral afferent via alpha 1 adrenergic receptors.
2. Noradrenalin exciting alpha 2 adrenergic receptors mediating the release of prostaglandins exciting the primary afferent fibre.
3. Sympathetic and sensory fibres coupled electrically via synapses or the lesser known ephapses either in the terminal region or between fibres within Remak bundles (aggregation of C fibres) resulting in 'cross talk' (Gasser, 1955).
4. Noradrenalin release may have local effects on blood flow, environment in skin enhancing activity.

While many autonomic nerves are purely sensory, certain primary afferent nerve fibres also have an efferent (and trophic) function. Sensory neurotoxins stimulate transmitters released at peripheral endings to produce vasodilation and smooth muscle contractility. Furthermore, they may have effects on the regional leukocytes and fibroblasts leading to what is known as "neurogenic inflammation", with eventual stimulation of somatic afferent fibres causing pain (Mense, 2004). This may explain many of the more severe musculo-skeletal and sensory symptoms affecting the patient with CFS/ME.

The general medical view, pre-1990's, was that the sympathetic nervous system was largely efferent, producing an array of disturbed physiological symptoms (Cunningham, 1973; Burn, 1971; Korr *et al.*, 1964, 1960, 1947). It is now accepted that the sympathetic nervous system has a large afferent component that sends disturbed messages to the central nervous system in cases of bodily distress and disease (see Fig. 31). The afferent nerves run alongside somatic sensory nerves throughout the body (Bonica, 1990). It is also now realised that autonomic diseases can occur in association with a broad range of neurological, cardiovascular, endocrine, and general medical disorders (Guyton and Hall, 1996; Bannister and Mathias, 1993).

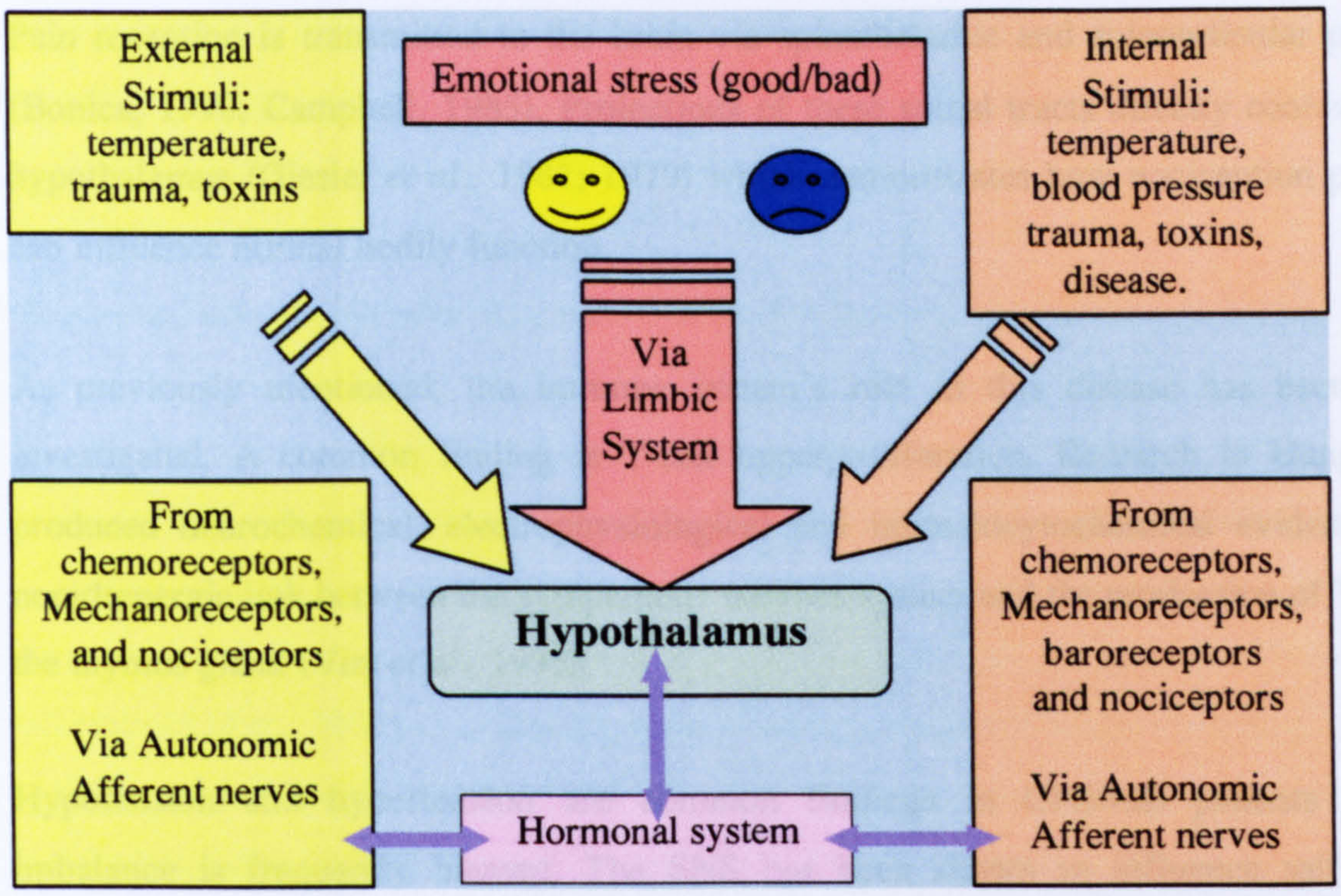



**Figure 31 The afferent (sensory) component of the autonomic nervous system**

A schematic diagram simplifying a complex interaction within the nervous and hormonal systems of the sensory component of the ANS. A barrage of messages are continuously sent to the hypothalamus from all manner of stimuli.

The errant sensory component of a disturbed sympathetic nervous system appears to be the main neurological feature seen in CFS/ME. This dysfunction may produce an increase or a reduction of sympathetic activity in the sufferer, often with hypo- and hyper-sympatheticonia affecting different target organs concurrently in the same patient, e.g. a patient may complain of increased perspiration, dryness of mouth and coldness of extremities simultaneously. This explains the multi-variant characteristics of this disorder. The role of the sympathetic nervous system (SNS) in the pathogenesis of CFS/ME can be demonstrated when examining other individual symptoms of the disorder. Most patients with CFS/ME have undergone some form of prior stress, whether it is physical, emotional, chemical or viral. That has obviously placed extra strain on the SNS (Noll *et al.*, 1996; Jansen *et al.*, 1995). Pain, in the joints, muscles or even viscera, is a frequent complaint of the patients. The sympathetic nerves are integrally related to the neurological pathways involved in the "pain system" (Bonica, 1990; Janig, 1988).

Pain reception is transmitted to the brain via spinothalamic and spinoreticular pathways (Bonica, 1990; Campbell, 1985). Projections of these spinal tracts directly connect to the hypothalamus (Giesler *et al.*, 1981; 1979) which demonstrates how nociception pathways can influence normal bodily function.

As previously mentioned, the immune system's role in this disease has been widely investigated. A common finding is T-cell hyperproliferation. Research in Hungary has produced neurochemical, electrophysiological and immunocytochemical evidence for a noradrenergic link between the sympathetic nervous system and the production of T-cells in the thymus gland (Vizi *et al.*, 1995).

Hypotension and hypertension are common findings in CFS/ME patients and salt imbalance is frequently blamed. The SNS has been shown to influence salt appetite (Bourjeili *et al.*, 1995). A dysfunction of the SNS could account for this finding. Another common complaint is an irritable bladder. This is possibly due to SNS effects on bladder pressure and afferent nerve activity from the bladder (Khadra *et al.*, 1995). Irritable Bowel Syndrome (IBS) is characterised by chronic bouts of alternating constipation and diarrhoea plus associated abdominal pain. The role of the SNS in gastric and bowel function is well documented (Iovino *et al.*, 1995). IBS is often reported in CFS/ME cases and may be due to changes in gastric and bowel control due to SNS dysfunction.

Experiments in the former Soviet Union demonstrated behavioural changes in rabbits after impairment of the functioning of the sympathetic nervous system (Sollertinskaia, 1957; Koramian, 1958). Following a sympathectomy, certain reflexes controlled by the central nervous system were shown to be diminished. This early work demonstrated 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 brain function. This could explain why psychological symptoms develop with the advancing CFS/ME.

An early symptom complained of in CFS/ME is hyperacusis (acute sensitivity to sound). A recent study showed that cervical SNS stimulation had a protective effect on the

susceptibility to acoustic trauma (Wada *et al.*, 1995). Thus a dysfunctional SNS may provide the explanation for this symptom. Likewise photophobia in CFS/ME may be due to pupil dilation caused by increased sympathetic activity.

Recent research supports the dual nature of the sympathetic dysfunction in this disorder. An increase of choline has been reported in the occipital cortex of CFS/ME sufferers (Puri *et al.*, 2002). Excess cholinergic neurotransmission due to sympathetic overload would result in toxic amounts of choline. Conversely in some CFS/ME patients there is clearly a reduction of cholinergic neurotransmission. Galanthamine hydrobromide interacts with the enzyme acetylcholinesterase, thereby increasing levels of acetylcholine in the brain (Chaudhuri *et al.*, 2000). In a placebo-controlled trial of galanthamine hydrobromide on 49 patients with CFS/ME, 43% of the 39 who completed the treatment reported a 50% beneficial change in fatigue, myalgia and sleep (Snorrasson *et al.*, 1991).

#### 2.5.3.1.2 Hormonal activity

Hormonal activation via the hypothalamic pituitary-adrenal axis in response to stressors was initially coined the General Adaptation Syndrome by Hans Selye (1946; 1936). The nucleus paragigantocellularis (PGi), a part of the ventromedial medullary reticular formation, sends signals into the midbrain area known as the locus coeruleus (LC). This is a major source of adrenergic axons and believed to be the brain's centre for vigilance and arousal increasing awareness of potentially harmful stressors. The PGi-LC system is thus very sensitive to pain. With prolonged somatic dysfunction often leading to repetitive nociceptive input, a consequential overstimulation of the PGi-LC may contribute to the chronic adaptive response that ensues (Aston-Jones *et al.*, 1990). Corticotropin-releasing hormone (CRH) is a neuropeptide released from the paraventricular nucleus (PVN) of the hypothalamus following stimulation of the locus coeruleus via adrenergic neuronal pathways. The PVN is a key area in regulating both the autonomic and endocrine systems. Thus activation of the LC-PVN pathway by stressors leads to an increase in activity of the sympathetic nervous system and enhanced output of the Hypothalamic-Pituitary-Adrenal (HPA) axis.

Recently published research (Papanicolaou *et al.*, 2004) to emerge from the US maintains that over 800,000 North Americans suffer from CFS/ME. The scientists of this study suggest that the responsibility for this disease lies in the neuroendocrine system.

Stressors affect neuroendocrine events via neurotransmitters and other neuro-immunomodulators (Auveneshine, 1997). Mounting evidence demonstrates that the interconnections between the CNS and the immune system via the HPA axis are bidirectional (Black, 1994).

The connection between somatic and sympathetic components is clearly observed in the disorder called reflex sympathetic dystrophy RSD. This is also known as 'algodystrophy' which is a sympathetically maintained form of sensitisation presenting with a unilateral dystrophic limb plus increased vascularisation, flushing and warmth, compared with the healthy side. The condition may arise through minor injury causing sensitisation of a nociceptor and the onset may be within hours of the initial insult and may take weeks to spontaneously resolve. Alternatively it may become a chronic condition being maintained by increased sympathetic activity reducing local blood flow, lessening the removal of sensitising factors and by stimulating the release of sensitising chemicals. Spinal cord changes may also occur which may further increase sensitivity (Bossi *et al.*, 1989; Schott, 1989).

The onset of CFS/ME is frequently linked to pre-morbid psychological stressors, categorising CFS/ME as a stress-related illness. The mere association between exposure to emotional stress and alterations in immune, endocrinological and central nervous function does not prove cause and effect. Unfortunately there has been too much emphasis on the role of psychosocial stressors, with the concept of a physical aetiology largely being ignored. CFS/ME occasionally presents as a genetic disease with multiple sufferers found in different generations of one family. Thus CFS/ME, although being a neuroimmune disorder with many differing aetiologies, may actually target genetically predisposed individuals" (Goldstein, 1993). Environmental and genetic factors will alter the rate of chemical metabolism (McKeown-Eyssen *et al.*, 2004) and may predispose the development

of multiple chemical sensitivity. The prognosis of diseases such as CFS/ME will depend on the many factors affecting the body's capability to eliminate toxins

Later chapters in this thesis aim to demonstrate that the immune malfunction featured in CFS/ME may arise from a relationship between hypothalamic dysfunction and a breakdown in the integrity of the lymphatic system.

In conclusion the results of the first stage of the study have shown that osteopathic treatment reduces the severity of symptoms in the patient group compared to the control group. The following section of the work (chapters 3, 4 and 5) attempts to assess the possible physiological basis for these improvements.

# Chapter 3

# 3 Assessment of the osteopathic method for the treatment of CFS/ME: Phase 2; Cerebrospinal fluid, lymphatics and CNS drainage

## 3.1 Introduction

The results of the first phase of the study clearly demonstrated a significant improvement in the symptoms of the CFS/ME patient following osteopathic treatment. The question arises as to the reasons for the apparent success of such treatment. Because of the plausible associations in the ANS and its control of lymphatic circulation attention was turned to the possible involvement of the spinal drainage systems, and in turn the CNS lymphatic drainage systems in general. The rationale was that the osteopathic manipulations were modifying these, thus enhancing the clearing of toxins or viral components from these systems. In the following sections brief overviews are given of the cerebrospinal fluid (CSF) and the lymphatic/CSF drainage systems of the CNS.

### 3.1.1 The cerebrospinal fluid

Since impaired drainage of CSF into the lymphatics lies at the root of the author's neurotoxic hypothesis of CFS/ME then it is crucial to understand the physiology of what Still (1902) termed 'The waters of the brain'. .

There are two main aspects of CSF to consider when assessing any physiological change that may take place in a disease process.

1. The chemical composition of the CSF.
2. The circulation of CSF in the spine and ventricular system.

#### 3.1.1.1 The composition of CSF

The CSF is a clear, colourless fluid containing inorganic salts similar to the blood plasma with a chloride level of approximately 720-750 mg/100ml. The glucose level is half that of blood around 50-85 mg/100ml and there is only a small amount of protein 15-45

mg/100ml. The only cells normally present in the CSF are 0-3 lymphocytes per cubic millimetre of fluid. The standard lateral recumbent CSF pressure is roughly 60 to 150 mm $H_20$ and is subject to increase following any strain or compression to the head and neck. The average total volume of CSF in the ventricles and subarachnoid space of an adult is in the region of 130ml.

The production of CSF takes place in the choroid plexus of the ventricular system and relies on the brain's ability to draw the necessary ions and solutes from the blood plasma. An efficient blood flow of at least four millilitres per minute per gram of tissue is required to maintain the necessary CSF output. Cerebral arterial supply has indeed been shown to be reduced in CFS/ME (Costa *et al.*, 1994). Hydroxyl and hydrogen ions together with positively charged sodium ions, negatively charged chloride and bicarbonate ions transfer over the blood brain barrier, altering the osmotic pressure leading to a diffusion of water into the ventricles. About 99% of CSF is water and the ion transfer is important to maintain a healthy environment for the brain to function normally.

### 3.1.1.2 The circulation of CSF

CSF is produced in the lateral ventricles passing into the third ventricle through the interventricular foramina and then via the cerebral aqueduct to the fourth ventricle. The movement is aided by arterial pulsations of the choroid plexus and ciliated cells lining the ventricles. From the fourth ventricle the CSF drains out via the lateral foramen of Luschka and median foramen of Magendie to the subarachnoid space. Slowly moving through cerebellomedullary and pontine cisterns, most of the CSF travels upward through the tentorium cerebelli to the inferior surface of the cerebrum flowing laterally and superiorly over each cerebral hemisphere. The rest moves inferiorly in the subarachnoid space down the spinal cord aided by cerebral and spinal arterial pulsations and vertebral movement (Fig. 32).

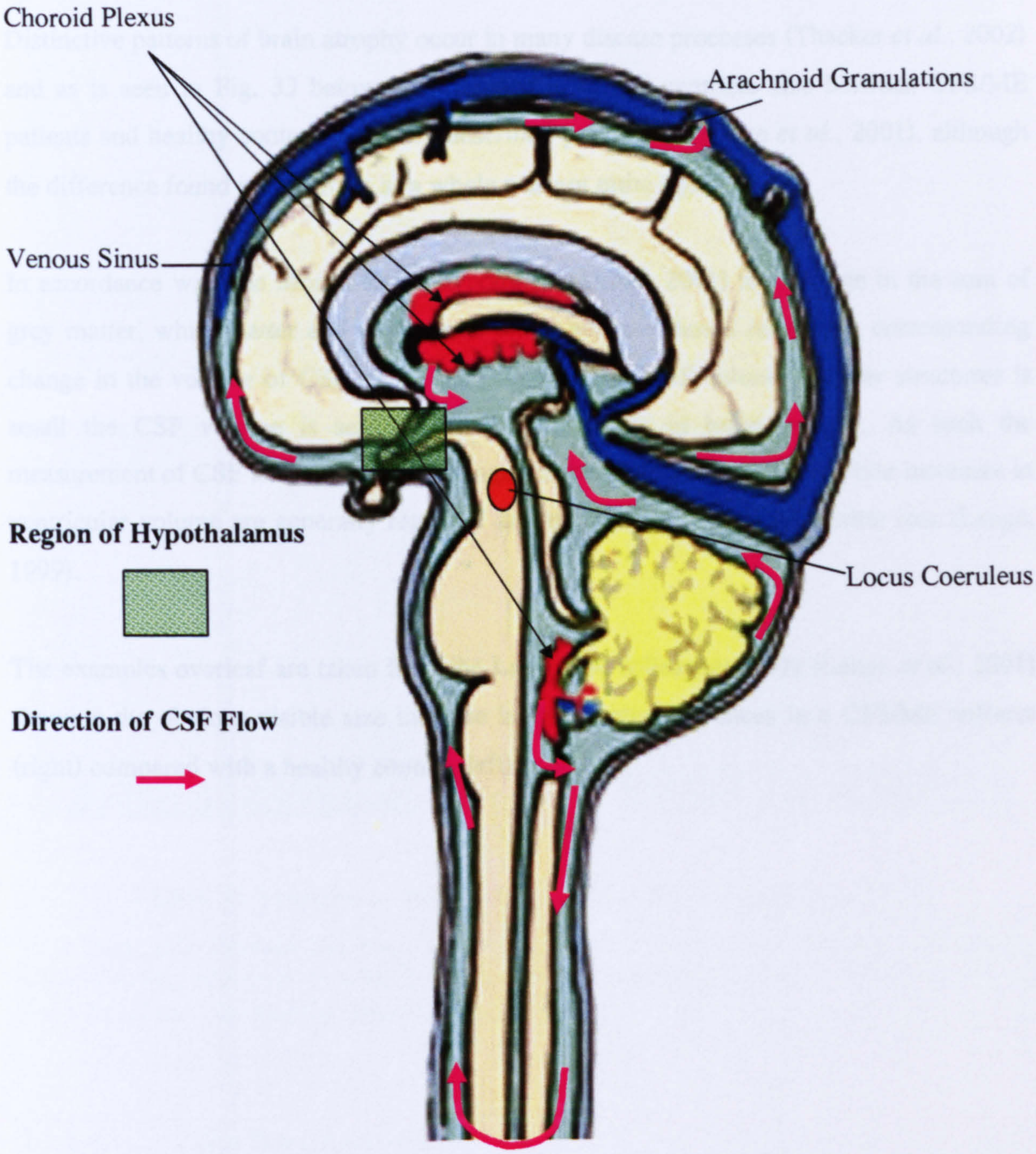



**Figure 32 Diagram showing cerebrospinal fluid flow**

(Drawn by the author based on original drawing by Netter in Felten and Joszefowicz, 2003)

The fluid's journey is shown from its production at the choroid plexus around the brain and spinal cord with most of the CSF draining into the venous sinuses. Further drainage also takes place via the extra-cerebral and extra-spinal lymphatics (see section 3.1.2).

### 3.1.1.3 CSF volume assessment by measurement of brain atrophy

Distinctive patterns of brain atrophy occur in many disease processes (Thacker *et al.*, 2002) and as is seen in Fig. 33 below, a difference in lateral ventricle size between CFS/ME patients and healthy controls has been described previously (Lange *et al.*, 2001), although the difference found in the group as a whole was not quite significant.

In accordance with the Monro-Kellie hypothesis (Mokri, 2001) any change in the sum of grey matter, white matter and intracranial blood volume should result in a corresponding change in the volume of CSF. Since the proportion of CSF volume to other structures is small the CSF volume is sensitive to small changes in brain volume. As such the measurement of CSF is used to detect changes in the brain tissue volume, while increases in ventricular volume are generally regarded as a measure of deep white matter loss (Lange, 1999).

The examples overleaf are taken from the Lange and colleagues study (Lange *et al.*, 2001) showing the obvious visible size increase in two contiguous slices in a CFS/ME sufferer (right) compared with a healthy control (left).

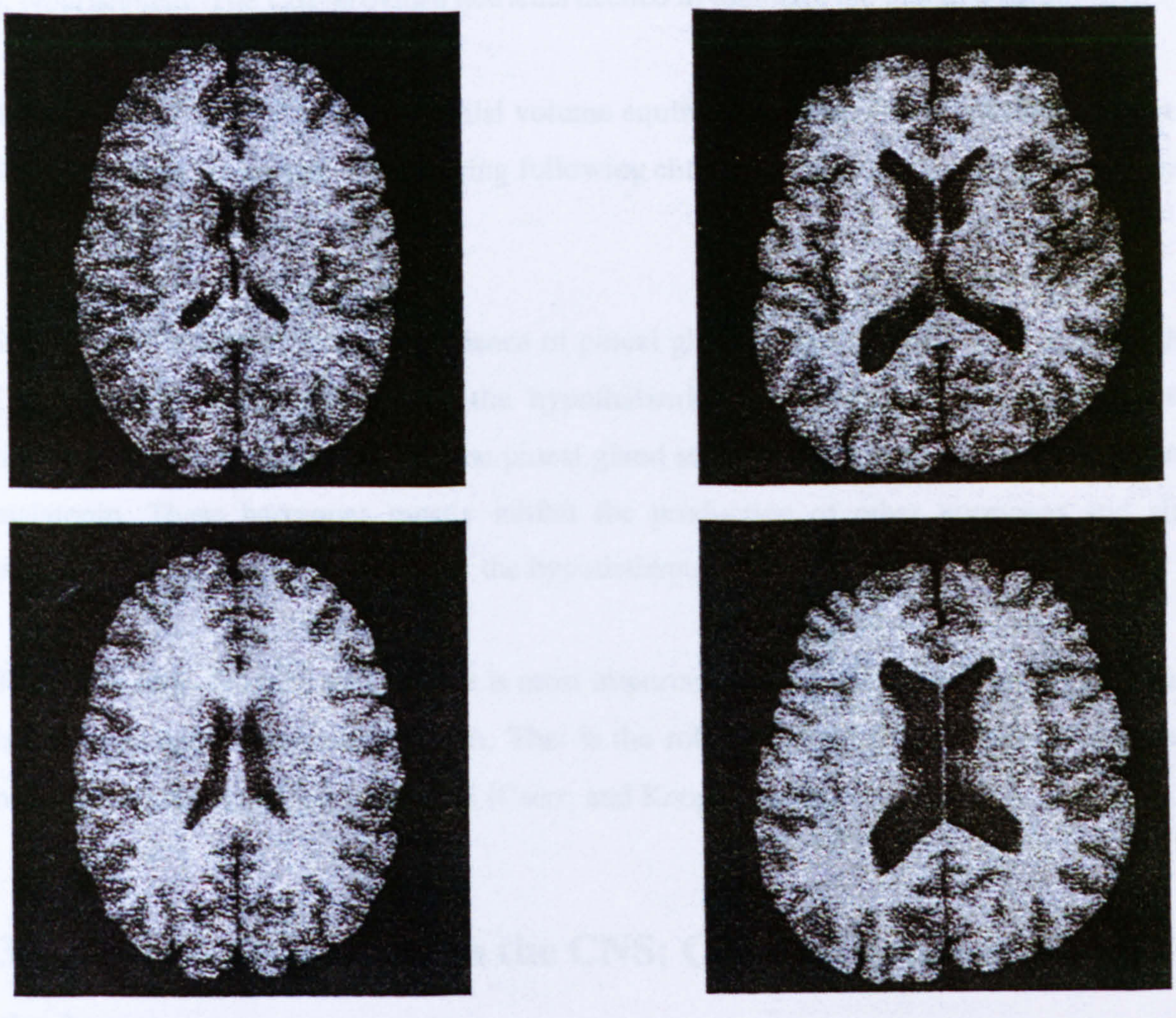


**Figure 33 Ventricular enlargement in CFS/ME (Lange *et al.*, 2001)**

Ventricular size increase has been seen in some CFS/ME patients compare with normal scans. The size of lateral ventricles in two contiguous slices in a cfs/me sufferer (right) are much larger than the healthy control (left).

### 3.1.1.4 The functions of CSF

There are five main functions of the CSF (Snell, 1995).

1. Protection of the CNS: The CSF provides a cushioning of the brain and spinal cord from external physical trauma.

2. Buoyancy: The CSF allows the brain to "float" giving support to its delicate structure.

3. Nourishment: The CSF provides nutrients needed to maintain the integrity of the CNS

4. Reservoir: The CSF aids intracranial volume equilibrium in accordance with the Monro-Kellie doctrine increasing or decreasing following changes in blood or brain volume (Greitz *et al.*, 1992).

5. Hormonal Medium: There is evidence of pineal gland secretions circulating through the CSF affecting the functioning of the hypothalamic-pituitary-adrenal axis. Sympathetic nerves release norepinephrine into the pineal gland stimulating the release of serotonin and melatonin. These hormones mostly inhibit the production of other hormones and also inhibit releasing factors produced by the hypothalamus (Kappers, 1976).

There is a sixth function of CSF that is most important to the pathogenesis of CFS/ME and has already been discussed at length. That is the role of aiding in the drainage of excess neuro-metabolites and toxin removal (Cserr, and Knopff, 1992).

### 3.1.2 Extracellular fluid in the CNS; CSF and lymphatic drainage

The perivascular space is formed between the blood vessels that supply the brain and the pia mater, as far as the arterioles and the venules but not the capillaries. CSF travels into the subarachnoid spaces flowing down to the arachnoid villi and is consequently absorbed into the cerebral veins (see Fig. 34).

As well as conveying fluid and traces of proteins, the perivascular space provides a thoroughfare for other particles, e.g., during infection in the brain, dead white blood cells and other infectious debris are transported away through the perivascular spaces (Guyton and Hall, 1996).

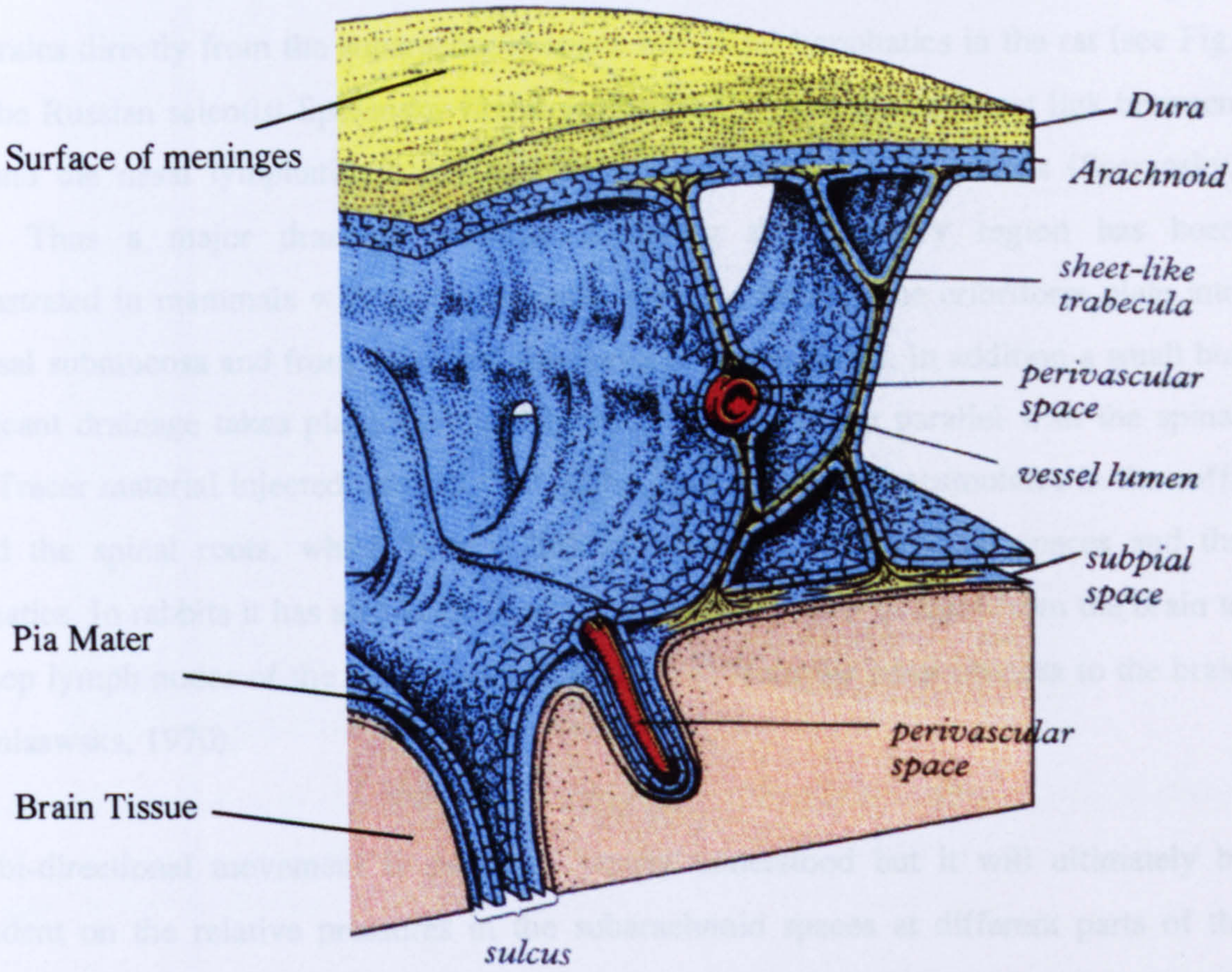



**Figure 34 Section of the meninges illustrating perivascular spaces**

(Illustration from Gray's Anatomy 38th Edition p.1213, Zhang *et al.*, 1990)

The diagram shows the perivascular space between the blood vessels that supply the brain and the pia mater.

The major reason for a secondary drainage system in the body is molecular size. The capillaries cannot absorb the larger molecular structures from the interstitial tissue via filtration through the blood vessel membrane. The lymph vessels take in any size of debris due to the mechanism outlined below.

Although it has been established that the CNS does not have a true lymphatic system, there is considerable evidence for a robust fluid drainage system, which in many ways is

analogous to the lymphatics. Relatively little is known for man, but quite comprehensive studies have been made on several experimental animals including rodents, rabbits and cats (Kida *et al.*, 1993).

CSF drains directly from the subarachnoid space into nasal lymphatics in the rat (see Fig. 36). The Russian scientist Speransky first described the existence of a direct link between CSF and the nasal lymphatics and onwards to the cervical lymph vessels (Speransky, 1943). Thus a major drainage pathway involving the olfactory region has been demonstrated in mammals with many channels draining through the cribriform plate into the nasal submucosa and from there into the cervical lymph nodes. In addition a small but significant drainage takes place via dural lymphatics, which run parallel with the spinal cord. Tracer material injected into the CSF in the brain of rabbits accumulates in the cuffs around the spinal roots, which form a link between the subarachnoid spaces and the lymphatics. In rabbits it has also been shown that there is a flow of fluid from the brain to the deep lymph nodes of the neck, and a flow of fluid from the nasal mucosa to the brain (Czerniaswska, 1970).

This bi-directional movement is relatively poorly understood but it will ultimately be dependent on the relative pressures in the subarachnoid spaces at different parts of the neuraxis and in the CNS parenchyma (McComb *et al.*, 1982). In the rabbit approximately 30% and in the cat 10-15% of the total normal CSF drainage occurs via these routes (Bradbury and Cole, 1980). It has also been shown that almost a half of the total volume of CSF in sheep drains into the extracranial lymphatics especially in the cervical region. Also the CSF drainage into the cervical lymphatic system rises with increased ICP (Silver *et al.*, 1999).

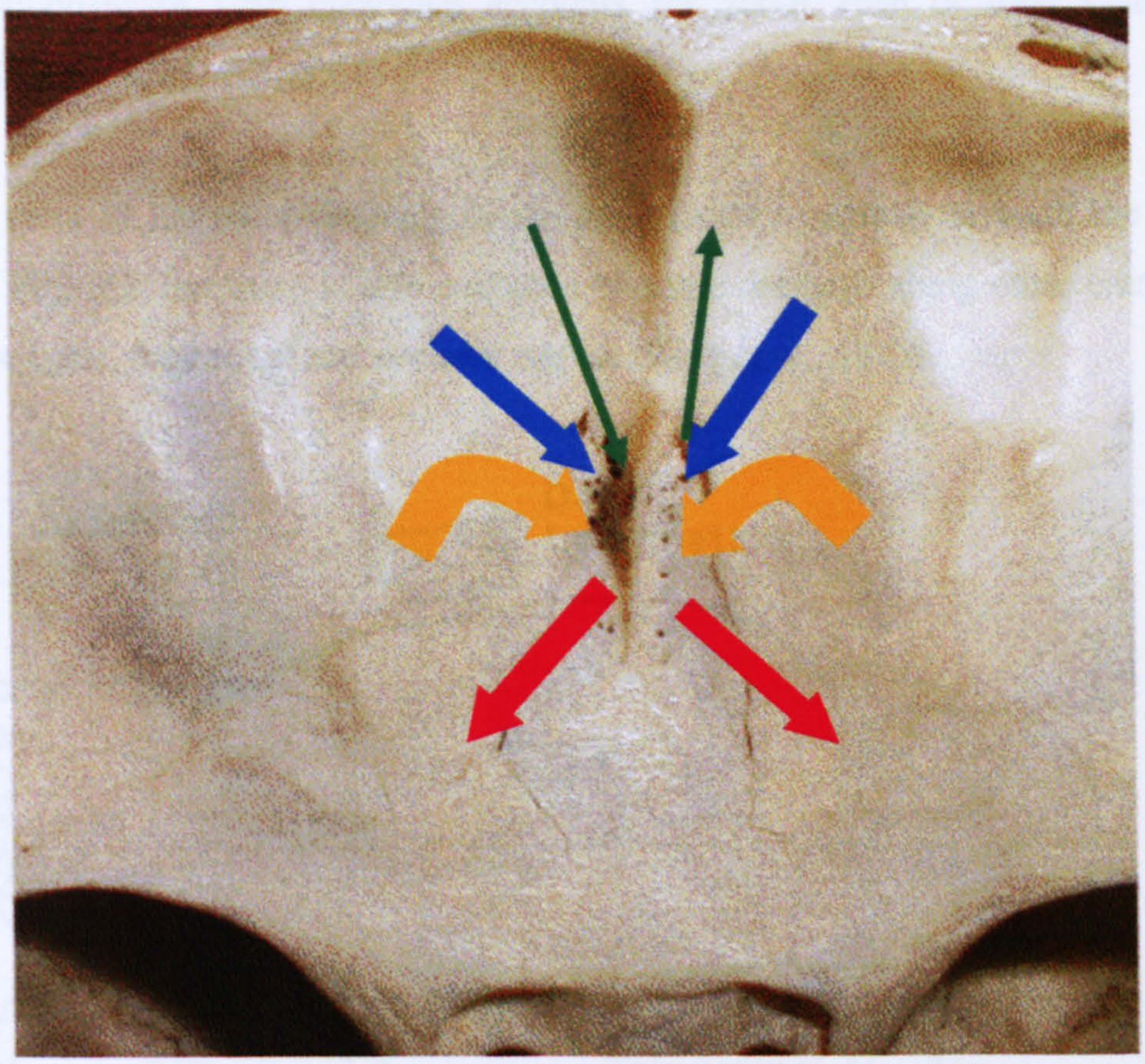


**Figure 35 Superior view of ethmoid showing the perforations in the cribriform plate**

= arterial supply = venous return = CSF drainage to lymph
= Nerves (both afferent and efferent).

The perforations seen above allow the passage of blood vessels, nerve fibres and the passage of CSF from the brain to the nasal sinuses situated directly below the ethmoid bone.

Of great interest is the demonstration that by tilting the angle of the experimental animal's head (angle of 20 degrees to horizontal), the drainage from brain to cervical lymph can be markedly increased; thus gravity affects the lymph flow (Simmonds, 1952). This drainage may further act as a valve to relieve ICP which would explain why pressure did not build up until the "break point" was reached in the study on hydrocephalic rats (Jones and Lopman, 1998).

Cerebrospinal fluid transport occurs down the spinal subarachnoid spaces as well as in the brain. CSF is drained out via microscopic spinal arachnoid granulations similar to the granulations in those found in the choroid plexus of the brain's superior sagittal sinus. The

spinal component of CSF clearance accounts for about 25% of total CSF transport (BozanovicSocic *et al.*, 2001).

Cranially most of the extra drainage is via the olfactory pathway through the cribriform plate (see Fig. 35), but there is also evidence of some drainage along other cranial nerves, namely the optic, trigeminal and acoustic nerves (Kida *et al.*, 1993).

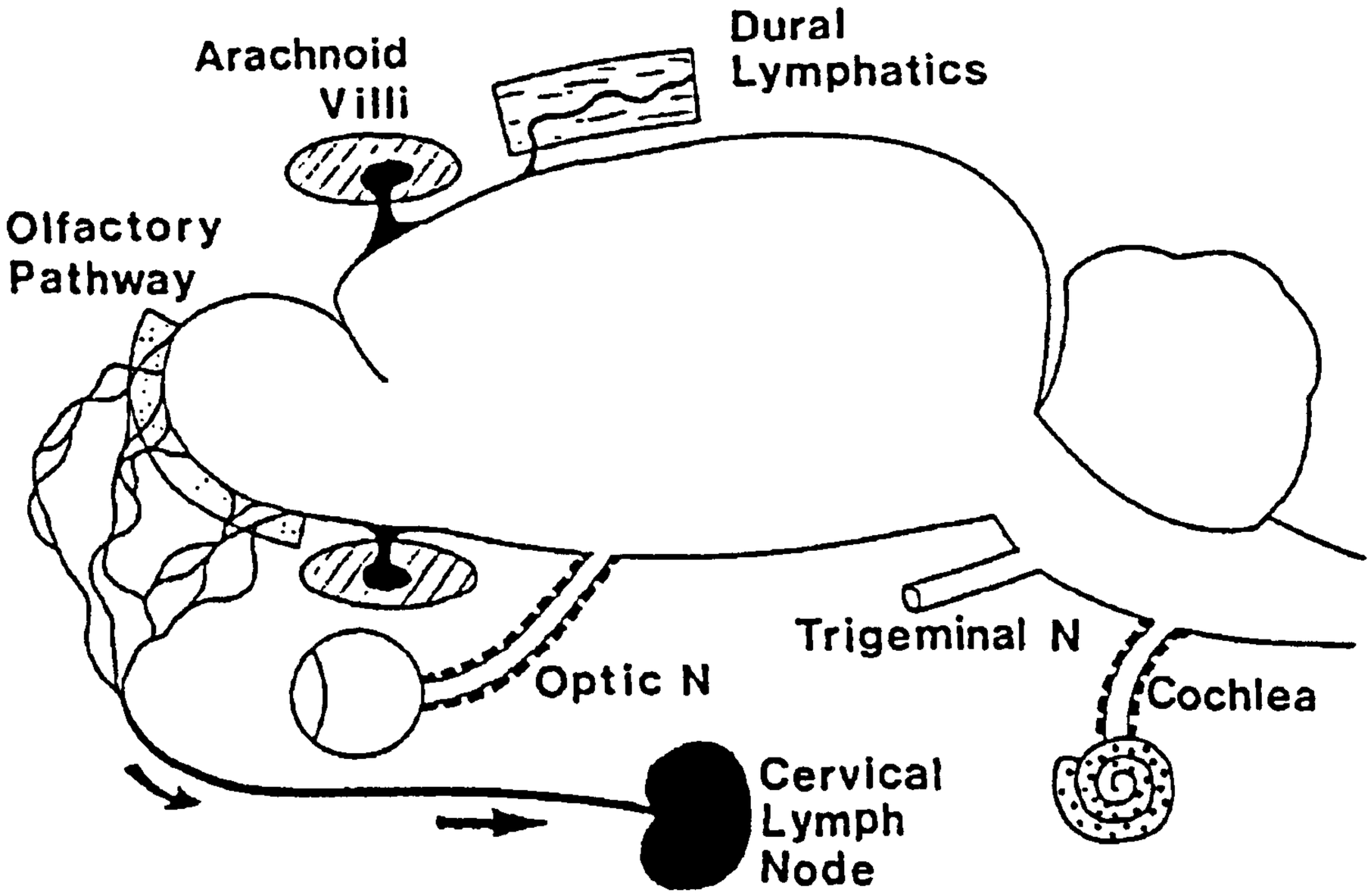



**Figure 36 The lymphatic drainage of the rat's brain (Kida *et al.*, 1993)**

Note that as well as through the arachnoid granulations directly to venous return, there is a potential substantial drainage of toxins from the cerebrospinal fluid through the dural lymphatics, and along the I, II, V and VIII cranial nerves to the cervical lymphatics.

Although the drainage pathways of CSF to facial and spinal lymphatics have been demonstrated principally in animal studies, more recent research examined this connection in the human (Cserr and Knopf, 1992; Czerniaswska, 1970; McComb *et al.*, 1982). In man recent evidence has shown that CSF can leave the CNS via several routes (Fig. 37) As in the animal studies, these include pathways from the cranial and spinal subarachnoid space across the arachnoid villi to the dural sinuses and along the cranial, mostly via olfactory

pathways through the cribriform perforations, and spinal nerves to the lymphatics (Knopf and Cserr, 1995).

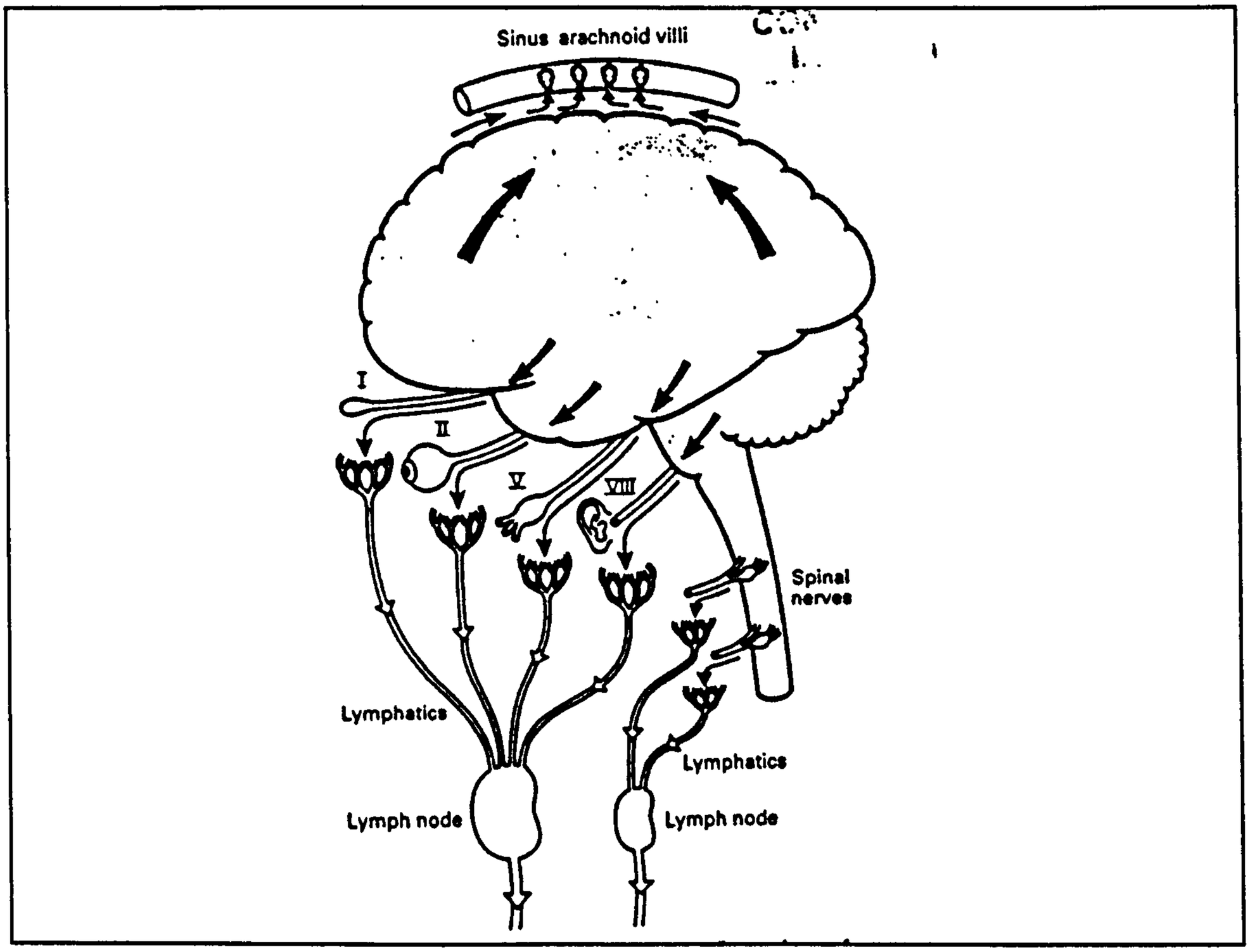



**Figure 37 Schematic demonstrating the lymphatic drainage of the human brain**

**(Knopf and Cserr, 1995)**

I= Olfactory II= Optic V= Trigeminal VIII= Acoustic

As well as drainage into the sinus arachnoid villi there is further passage of CSF down the spine into the paravertebral lymphatics and alongside the cranial nerves shown in the diagram. The CSF then flows into the facial, cervical and eventually into the thoracic lymphatics.

The system of CSF drainage in man is believed to be very similar to other mammals except the CSF-lymphatic component is proportionally much smaller in humans. The above drainage of CSF would indicate increased CSF volume may not necessarily cause an immediate increase in ICP with all the associated symptoms. There may very well be a "break point" in humans as with animals.

Cerebral hypotension may be just as symptomatic as an increase in ICP with orthostatic headaches common but not always present when there is over-drainage of CSF (Mokri *et al.*, 2000). Postural headaches most often occur after a lumbar puncture where the procedure reduces ICP.

Palpation of the cranial flow in all members of the patient group indicated that there was a reduction in the normal rhythm of CSF. This palpably reduced flow may possibly be the result of reduced CSF flow into the lymphatics leading to a build up of toxic debris which would affect the normal functioning of the brain cells.

## 3.2 Aims of phase 2

The overall aims of the second stage are to examine the involvement of alterations in CSF flow and drainage into cervical and thoracic lymphatics in the aetiology of CFS/ME and further study the effects of osteopathic treatment. The close association of the treatment with a potential underlying anatomical and physiological pathway is strong argument for such a study. It is intended to analyse any recordable physical changes taking place within the CSF pathway and or lymphatic drainage of the neuraxis. The results of this analysis will be compared with similar measurements on two control groups, one group consisting of CFS/ME patients not receiving osteopathy, and the second control group made up of healthy norms. The possible involvement of CSF drainage into the CNS lymphatics has not yet been evaluated in the CFS/ME patients.

## 3.3 Patients and methods

As in the first phase the study design for this section was repeated measures, although this part was a comparative study of three groups as opposed to two in phase 1. Also all the participants in this stage, including the controls, were subjected to the same tests and analyses carried out under the supervision of the author.

### 3.3.1 Participant recruitment

Volunteers were recruited using adverts placed in local and national press with the first nine patients who fulfilled the CDC criteria (Fukuda *et al.*, 1994) selected to be on the treatment group; these were only accepted after independent corroboration from their GP. It was also important to ensure that the diagnosis of CFS/ME was confirmed by independent medical opinion. Therefore the subjects in this study had all been validated as having no other possible patho-physiological cause of the symptoms and were all certified by their GP as having no other coexisting pathology and fulfilling the CDC criteria (Fukuda *et al* 1994).

The inclusion and exclusion criteria were the same as those used in phase 1 (see sections 2.2.1. and 2.2.2), except that in phase 2 the patients did not pay for their treatment. The control groups consisted of age, gender, height and weight matched CFS/ME sufferers not receiving manual treatment and healthy subjects. The demographic data of each individual subject is listed in Table 12 and summarised in Table 13. All subjects followed the same recruitment procedures as the treatment group. Subjects were only included if they were aged between 18 and 55 and not pregnant and were not included if they had received any physical therapy for their present symptoms during the previous six months.

The CFS/ME patients were divided into 2 groups, the first group (**CFS1**, 5 men and 4 women: age range 20-53 years; mean age 35.3 years ± 12.6 [SD]) received only an osteopathic treatment for 1 year (see Table 12A), while patients in the other group, (**CFS2**; 5 men and 4 women: age range 22-55 years; mean age 36.1 years ± 12.3) were allowed to pursue treatment regimes of their own choice, excluding osteopathic treatment (see Table 12B). None of the CFS patients were considered to be from the extreme end of the symptomatic spectrum (i.e. bedridden, with intense sensitivity to any external stimuli). The control group (**NORM**, 5 men and 4 women: age range 22-53 years; mean age 36.1 years ± 12.4) were normal volunteers in good general health and with no history of significant neurological abnormality (see Table 12 C).

| Code | Gender | Age/Yrs. | Wt./ kg | Ht./m |
|---|---|---|---|---|
| RV01 | F | 29 | 69.9 | 1.8 |
| RV03 | M | 28 | 82.6 | 1.88 |
| RV04 | M | 43 | 85.7 | 1.83 |
| RV05 | M | 53 | 95.3 | 1.88 |
| RV06 | F | 19 | 81.6 | 1.8 |
| RV07 | F | 42 | 58.1 | 1.52 |
| RV08 | M | 22 | 79.4 | 1.83 |
| RV09 | M | 52 | 101.6 | 1.8 |
| RV10 | F | 27 | 44.5 | 1.58 |
| Standard Deviation | | 12.75 | 17.80 | 0.13 |
| Mean | M:F= 5:4 | 35 | 77.6 | 1.77 |

A. CFS/ME Patients receiving manual treatment (CFS1)

| Code | Gender | Age/Yrs. | Wt./ kg | Ht./m |
|---|---|---|---|---|
| CP01 | M | 43 | 78.5 | 1.78 |
| CP02 | F | 43 | 66.2 | 1.63 |
| CP03 | F | 29 | 73 | 1.63 |
| CP04 | M | 52 | 95.3 | 1.78 |
| CP05 | M | 26 | 69.9 | 1.83 |
| CP06 | F | 24 | 63.5 | 1.73 |
| CP07 | M | 54 | 81.6 | 1.75 |
| CP08 | M | 29 | 92.1 | 1.98 |
| CP09 | F | 20 | 66.7 | 1.68 |
| Standard Deviation | | 12.62 | 11.48 | 0.11 |
| MEAN | M:F=5:4 | 35.6 | 76.3 | 1.75 |

B. CFS/ME Patients not receiving any manual treatment (CFS2)

| Code | Gender | Age/Yrs. | Wt./ kg | Ht./m |
|---|---|---|---|---|
| NC01 | M | 52 | 79.4 | 1.78 |
| NC02 | M | 53 | 85.7 | 1.79 |
| NC03 | F | 30 | 61.2 | 1.6 |
| NC04 | F | 41 | 95.3 | 1.73 |
| NC05 | M | 26 | 83.5 | 1.87 |
| NC06 | M | 44 | 78 | 1.78 |
| NC07 | F | 19 | 52.6 | 1.62 |
| NC08 | M | 24 | 88.9 | 1.85 |
| NC09 | F | 29 | 73 | 1.58 |
| Standard Deviation | | 12.49 | 13.51 | 0.11 |
| MEAN | M:F=5:4 | 35 | 77.5 | 1.73 |

C. Healthy subjects (NORM)

**Table 12 Demographic data of subjects (phase 2)**

As shown in Table 12 all three subject groups were all gender, age, weight and height matched. The subjects were all instructed to try and maintain their weight at the start of the project for the year-long trial. A summary of the data listed in Table 12 A, B and C is shown in the chart below (Table 13).

| | Gender M:F | Age (years) mean (range) | Weight (kg) Mean (s.d.) | Height (m) mean (s.d.) |
|---|---|---|---|---|
| Treated patients (CFS1) | 5:4 | 35 (19-53) | 77.6 (17.8) | 1.77 (0.19) |
| Non-treated patients (CFS2) | 5:4 | 36 (20-54) | 76.3 (11.48) | 1.75 (0.11) |
| Healthy norms (NORM) | 5:4 | 35 (19-53) | 77.5 (13.51) | 1.73 (0.11) |

**Table 13 Summary of demographic data (phase 2)**

As shown the three subject groups were all gender, age, weight and height matched. The numbers in brackets in column 2 are the range of age in the different groups. The numbers in brackets in the 3rd and 4th columns give the standard deviations for mean weight and height, which were similar in all three groups.

To ensure that the no volunteer was suffering from a unipolar depression or primary anxiety state all the subjects who volunteered were included only after being independently approved of by a consultant psychiatrist as suffering with CFS/ME, and not in any depressive or anxiety state. The psychiatrist conducted an hour long consultation with each subject, using both the Hospital Anxiety and Depression Scale (HADS) (Moorey, 1991; Zigmond and Snaith, 1983) and the much more precise Schedules for Clinical Assessment in Neuropsychiatry (SCAN) which via a set of instruments provides a comprehensive, accurate and technically specific means of describing and classifying psychiatric phenomena (Mavreas, 1990; Tomov and Nikolov, 1990; Ustan, 1990; Wing, 1990).

The HADS system is an inventory of 14 questions half examining the depression, the other half anxiety. The subjects were asked to score 0 to 3 depending on the severity of how they felt in the previous week, with a total score of over 10 signifying a state of anxiety and/or depression (See Appendix A3).

The SCAN system is a set of instruments and manuals aimed at assessing, measuring and classifying the psychopathology and behaviour associated with the major psychiatric disorders of adult life. The SCAN text has 3 components: the tenth edition of the Present State Examination (PSE10), the Item Group Checklist (IGC) and the Clinical History Schedule (CHS).

PSE10 itself has two parts. Part I covers somatoform, dissociative, anxiety, depressive and bipolar disorders, and problems associated with eating, alcohol and other substance abuse. There is also a screen for Part II conditions. Part II covers psychotic and cognitive disorders and observed abnormalities of speech, affect and behavior.

The SCAN system contains two other essential elements: the Glossary of differential definitions and CATEGO, a set of computer programs for processing SCAN data and providing output (see Appendix A3 for more details of SCAN)

The use of the above exclusion criteria reduced, as much as possible, any chance of a psychiatric disorder being responsible for the symptom picture in the patients, and confirmed that the diagnosis of the cohort of eighteen CFS/ME sufferers was as robust as possible.

## 3.3.2 Treatment

The manual treatment of each CFS/ME research volunteer, RV01-9 followed the same technique protocol of the first phase (see section 2.2.4.6) (Stoddard, 1982; Hartman, 1983).

## 3.3.3 Symptom assessment

Change in the condition of each patient was assessed using the same eight self-report questionnaires as in phase one (Appendix A6). These were filled out by all 27 members of the patient and control groups and a further set of questionnaires were completed by the subjects after twelve months.

## 3.3.4 MRI analysis of the brain and associated lymphatics

MRI was performed by means of a 1.5 Tesla whole body scanner (ACS-NT PT 6000, Phillips Medical Systems, Best, Netherlands), using a birdcage head coil receiver, in the imaging science department of the University of Manchester (See Fig. 38). MRI was performed at the start of the study and was repeated after 90 minutes rest to ensure reproducibility. All imaging was repeated after 1 year to assess longitudinal changes.

**Figure 38 The Philips MRI scanner at the University of Manchester**

The patient remained supine with wedge under knees throughout all the scan sequences and sound defenders or foam was placed over their ears.

The work involved the development of some novel image and numerical analysis procedures in addition to those already used for imaging of intracranial and spinal CSF-circulation (Detre *et al.*, 1995). A series of MRI scans were made at the start and again at the end of the twelve months programme.

### 3.3.4.1 Why choose MRI?

MRI studies have already demonstrated that small discrete, patchy brain stem subcortical lesions can often be seen in CFS (Keenan, 1999; Lange *et al.*, 1999). However SPECT and

SPET studies have shown cerebral blood flow reductions in CFS, in particular in the hindbrain (Ichise *et al.*, 1992; Costa *et al.*, 1994).

Positron emission tomography (PET) has an advantage compared with other imaging techniques in that technological advances in this method permit direct visualisation and quantitative measurements of neurotransmitters in the brain (Brooks *et al.*, 1990), yet it is extremely expensive and too invasive. PET and SPECT (single photon emission computed tomography) scans can be used to determine the amount of cerebral circulation in the patient (Ibanez *et al.*, 1995). Until recently the only accurate measurements of blood flow within the capillary beds of the brain were indeed performed using radioactively- labelled water molecules and PET.

SPECT (single photon emission computerised tomography) has been also used to measure cerebral blood flow combined with 99mTc HMPAO, a tracer which is highly lipophilic and passes into the brain in quantities proportional to the regional blood flow. However this method exposes the patient to radiation and produces low spatial resolution images with no other anatomical data, thus one must also combine SPECT with other cross sectional imaging techniques such as MRI or CT. Xenon enhanced CT provides a high resolution anatomical and accurate flow image, but uses high levels of radiation and presents other clinical difficulties due to anaesthetic properties of xenon.

Magnetic Resonance Imaging (MRI) scans can also determine the amount of cerebral blood flow and offer non- invasive *in vivo* measurement of structure-function relationships of the brain (Toft *et al.*, 1995). They are more available and less costly than the PET or SPET techniques. They can be used repeatedly without any known harmful side-effects, whereas the PET and SPET techniques produce too great a level of radiation to be repeated frequently. MRI scans have also been successfully utilised in previous studies to analyse cerebrospinal fluid (CSF) volume changes (Vogels, 1995). The MR scan of CFS/ME patients before and after treatment would reveal any volume change in CSF. Previous studies aimed at qualitative and quantitative assessments of lateral ventricular volumes

have revealed evidence of subtle structural changes of some patients with CFS/ME (Lange *et al.*, 1999).

### 3.3.4.2 The scanning procedure

The scanning procedure of the patient group was as follows:

1. Scan.
2. Rest for 90 minutes.
3. Repeat scan.
4. Rest for one hour followed by half an hour of osteopathic treatment.
5. Repeat scan.

This procedure was carried out at the beginning and end of the year-long treatment programme.

Both control groups received a scan followed by a rest period for 90 minutes then a further scan. This procedure was also carried out at the start and end of the project. The repetition of the scans and comparison with controls was to show if there was any change in the CSF and/or lymph volume and flow due to manual intervention and not a just a normal occurrence.

### 3.3.4.3 Sequences

Morphological imaging consisted of inversion recovery and T1 weighted gradient echo images to measure CSF volume changes and allow segmentation of cerebral tissues and measurements of cerebral structures.

The examinations were conducted by Professor Alan Jackson, the consultant neuroradiologist heading the project's Manchester University MR Scan team. To reduce bias, the images were viewed blind in that Prof. Jackson was unaware which group the subjects belonged to.

The severity and distribution of deep white matter hyper-intensities (DWMH) was assessed by Prof. Jackson using the objective scoring scale described by Scheltens and co-workers

(1993). Scoring was performed from matched FLAIR and inversion recovery images. All examinations performed prior to follow up, consisting of 2 examinations per subject, were scored in random order with the scorer blind to the diagnosis. Follow up scans were scored by the same observer who remained blind to the diagnosis. Following this, direct comparison was performed between initial and follow-up scans to identify changes in individual DWMH to which the scoring system might be insensitive.

Vessel localisation in flow velocity images was performed by manual selection of a small rectangular region of interest (ROI) in the centre of each vessel. The mean grey level (and hence flow velocity) was measured for each time point in the cardiac cycle. The resultant time curve of mean velocity for the ROI was then correlated with the corresponding time curve for every pixel in the image set. This resulted in a correlation image, where each pixel represented the correlation coefficient *r* of the waveform for that pixel location, with the waveform of the selected ROI. This image was then thresholded at an empirically determined value of 0.9 to determine the boundaries of each vessel. Flow through the vessels was calculated from heart rate, mean velocity and cross sectional area. Cerebral blood flow was calculated as the sum of the carotid and basilar flows. Between group comparisons were made of the total cerebral blood flow per minute, the proportion of the cycle through which CSF flow through the aqueduct was in the caudal direction (during systole), the total CSF flow in the caudal direction, the total CSF flow in the craniocaudal direction, the net CSF flow per cycle, the maximum craniocaudal CSF flow rate and the arterial to aqueduct delay defined as the time between the centre of the systolic peaks of the arterial and aqueductal flow velocity curves

#### 3.3.4.3.1 Multistack survey of head

Initially an axial T1 sequence was used (see Fig. 39). The FH (foot-head axis) was offset at 0. A check was made to ensure that the field of view FOV covered the area of the region of interest ROI. AP and RL offsets were changed to achieve this without changing the angle. The patient was repositioned to the centre of the head coil and a peripheral pulse unit (PPU) was applied to the finger of the patient, which was needed when examining cerebral blood flow in the carotid basilar phase contrast (see section 3.3.4.3.5).

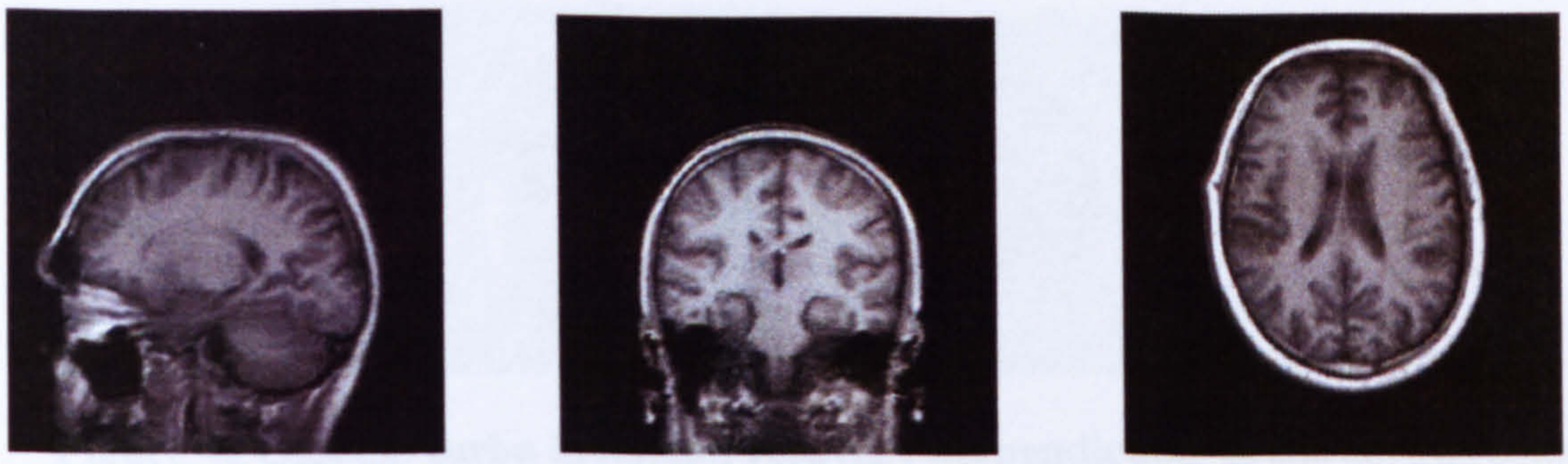



**Figure 39 Multistack survey T1 sequence**

Three views of the entire brain using T1 weighting. In a T1 contrast image fat, having a high signal appears bright, whereas water gives a low signal appearing dark on the T1 contrast images.

#### 3.3.4.3.2 Coronal turbo inversion recovery sequence

This sequence was to examine the structure of the white matter contrasting greatly with the dark ventricular system (see Fig. 40). This was the choice sequence to analyse the degree and distribution of cerebral atrophy by examining both the volume of all the CSF within the skull vault of the prosencephalon and the volume of CSF within the lateral ventricles.

The sequence for measurement of cerebral atrophy consisted of serial coronal fast spin-echo inversion-recovery images where the TR = 6,850 msec, TE = 18 msec, TI = 300 msec, echo train length = 9, field of view = 150 $mm^2$, matrix = 256 x 256, slice thickness = 3 mm and the interslice gap = 1 mm.

A. Frontal B. Parietal C. Temporal D: Occipital

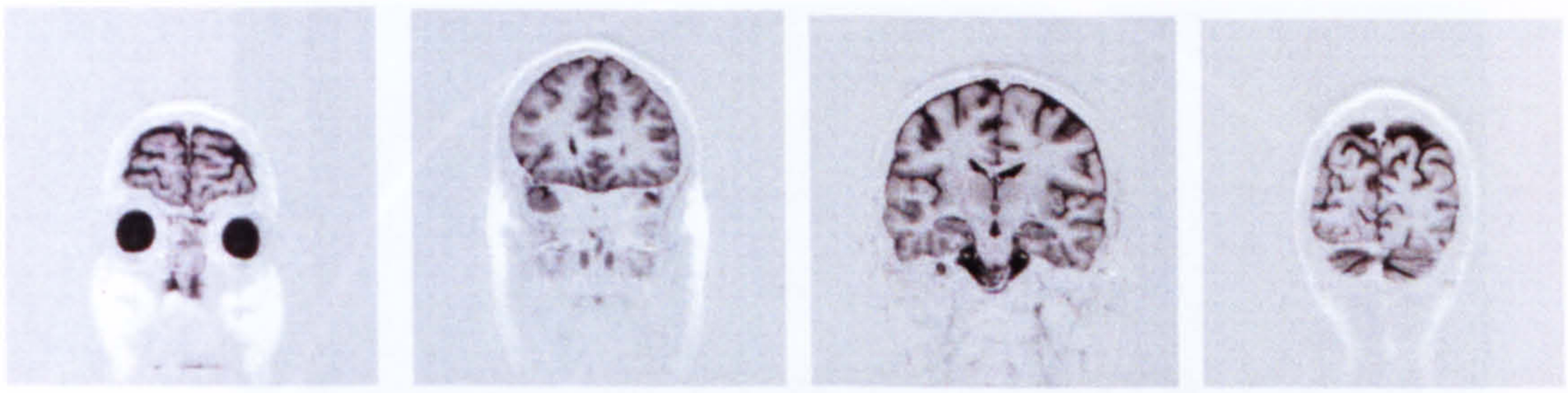


**Figure 40 Coronal turbo inversion recovery perpendicular to the corpus collosum**

A short turbo factor decreases effective TE, increases T1 weighting, has a longer scan time plus has more slices per TR. It is effective in reducing the image blurring. An inversion recovery sequence (IR) is used to produce a heavily T1 weighted image where there is a high contrast between fat and water. The lateral ventricles (image C) thus appear black.

### 3.3.4.3.3 Coronal FLAIR (fluid attenuated inverse recovery).

The presence of diffuse white matter or grey matter lesions was imaged using an optimised fluid attenuated inversion recovery FLAIR sequence (see Fig. 41). The following coronal images of different regions of the brain were used to determine the number and severity of any deep white matter hyperintensities. These are inversion recovery sequences acquired with a long T1 time to suppress signal from CSF. The grey matter on these images is brighter than the white matter. The coronal FLAIR sequence obtained for assessment of WMHs had a TR = 11000 msec, TE = 140 msec, TI = 2600 msec, with the image geometry identical to the previous sequence. The 4 different regions of the brain were examined separately for white matter hyperintesities and scored in the Scan Table 1 (section 3.4.2.2).

A. Frontal B. Parietal C. Temporal D: Occipital

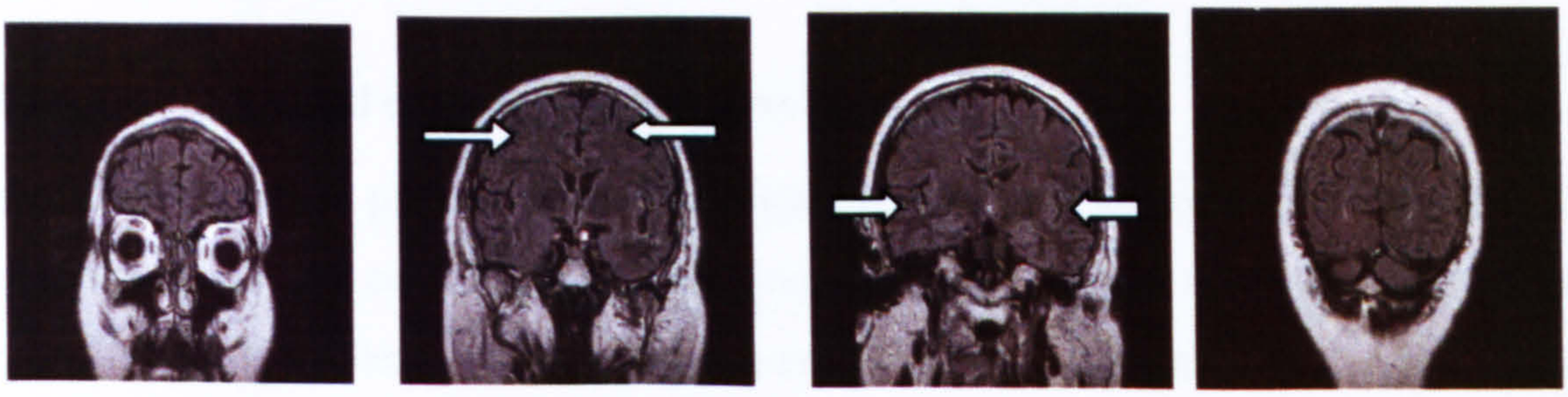


**Figure 41 Coronal FLAIR sequence perpendicular to the corpus collosum**

The usually high CSF signal in the T2 weighted images above are suppressed using a process known as FLAIR to allow pathological changes in adjacent tissue to be more visible. (The arrows point to the ROI in the different coronal images).

DWMH are seen in major cerebral neuropathology as shown in the FLAIR image below of a 20 year old woman with multiple sclerosis (Fig. 42).

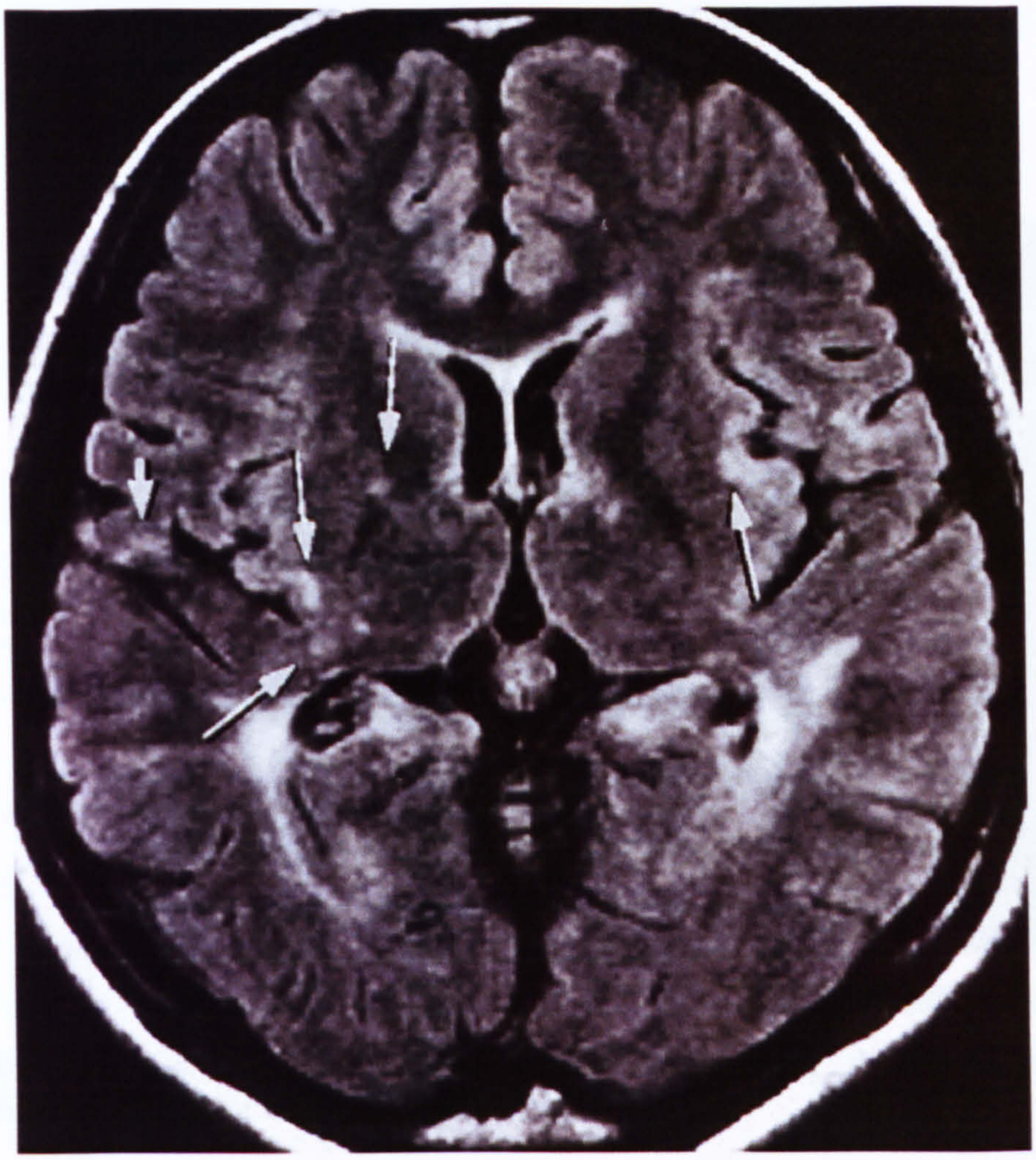


**Figure 42 Multiple DWMH shown in axial FLAIR images in a 20-year-old woman with MS (Okuda *et al.* 1999)**

MS plaques are seen on the image above as patches of varying hyperintensity indicated by white arrows. Note that the grey matter on a FLAIR image is brighter than the white matter.

### 3.3.4.3.4 Phased contrast angiography

A sequence known as phased contrast angiography was used to produce quantitative flow measurements in the carotid and basilar arteries to provide an estimate of the overall cerebral blood flow. Flow velocity images were produced using flow sensitivity in each of the cardinal directions and cardiac gating to produce 15 time points in the cardiac cycle.

Below is a sagittal image of the cerebral circulation of one of the healthy subjects showing important anatomical points (Fig. 43). Relevant to this current study is the position of the basilar and internal carotid arteries which were used to measure the cerebral blood flow utilising quantitative phase contrast angiography.

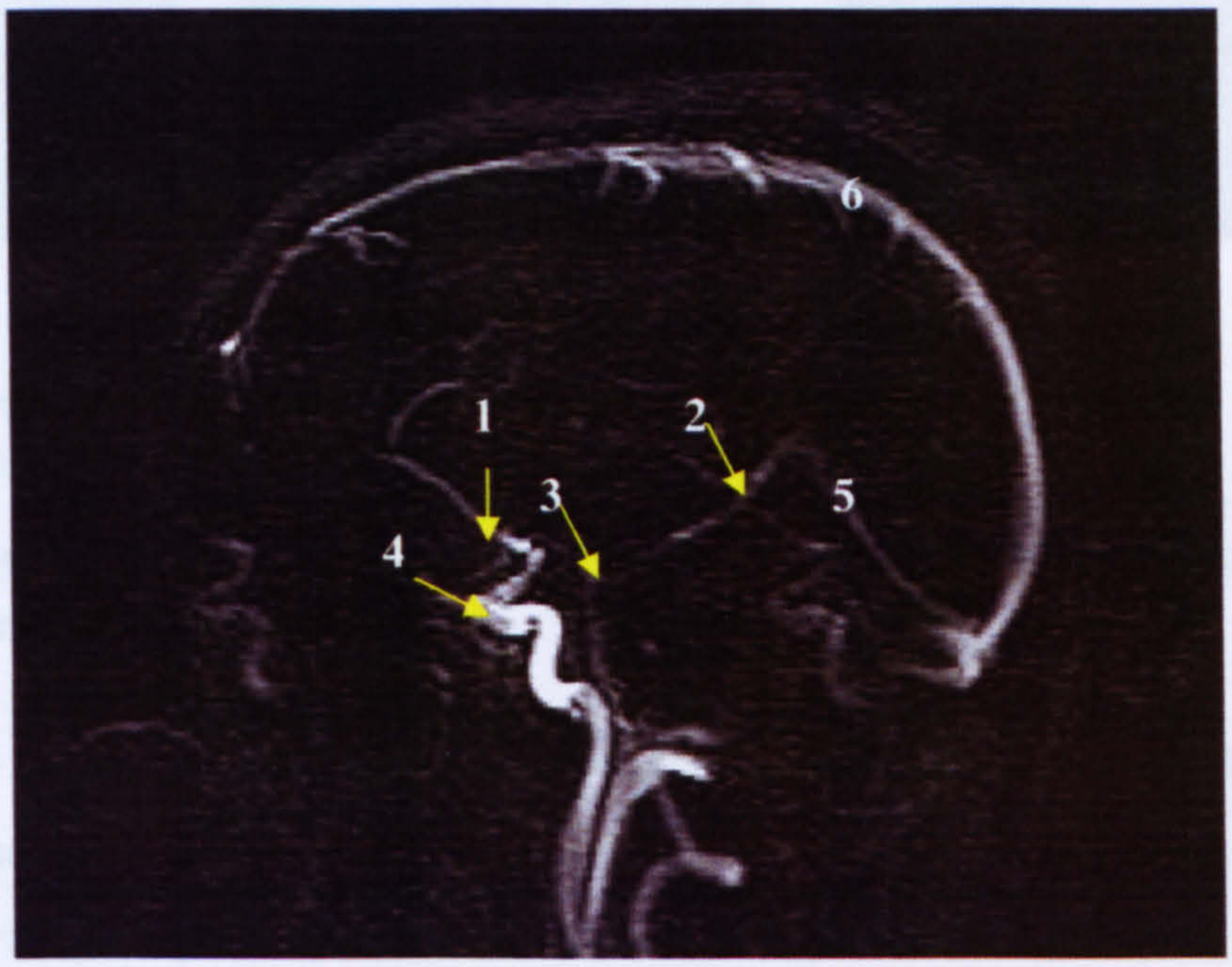



**Figure 43 Sagittal image of the cerebral circulation**

1. Cavernous sinus 2. Internal cerebral vein 3. Basilar artery 4. Internal carotid artery 5. straight sinus 6. Superior sagittal sinus.

### 3.3.4.3.5 Carotid basilar phase contrast (CAB PC)

Quantitative phase contrast angiography was used to measure total cerebral blood flow in a single slice at a position perpendicular to the internal carotid and basilar arteries with a TR = 5.66-5.86 msec, TE = 3.45-3.60 msec, flip angle = 15°, velocity encoding profile = 90cm.$s^{-1}$, field of view = 150$mm^2$, matrix = $64^2$ and slice thickness = 6 mm. Below are axial images perpendicular to the carotid and basilar arteries on the phase contrast survey.

A phase contrast image is created by producing a gradient in the magnetic field scanning the body followed by a second field gradient in the opposite direction cancelling them except if there is movement and will thus produce a signal which is proportional to the flow rate (see Fig. 44).

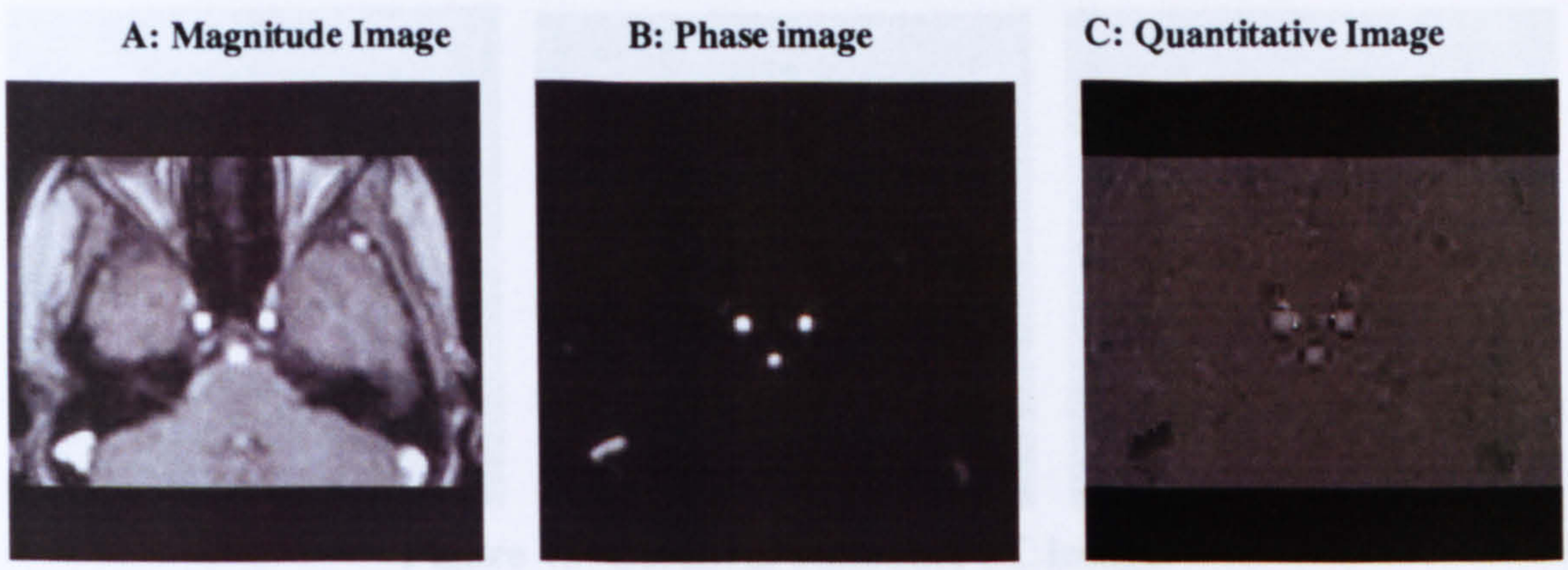



**Figure 44 The formation of a CAB PC Image.**

The magnitude image (A) shows the anatomical detail of the ROI, in this case the brain stem, where the right and left internal carotid arteries join the Circle of Willis (the two superior and lateral hyperintensities). The basilar artery is the central lower hyperintensity. The phase image (B) shows the presence of flow in these arteries. In the quantitive image (C) the flow is actually measured.

The signal intensity in the quantitative image is linearly proportional to the exact flow rate. The PPU, a light sensor attached to the patient's finger, detected the pulsation of blood through the capillaries. The pulsation was used to trigger the excitation pulses so that each slice acquired was at the same phase of the cardiac cycle. This technique known as peripheral gating is a method of reducing phase mismapping from the periodic motion of the cardiac cycle.

#### 3.3.4.3.6 Cerebral aqueduct PC

To examine and quantify CSF flow, a phase contrast sequence was initiated perpendicular to the cerebral aqueduct (Fig. 45) Again the cardiac frequency was changed in motion. The CSF flow through the cerebral aqueduct was scanned using a TR = 26.5msec, TE = 7.8 msec, flip angle =15°, velocity encoding profile = 5 $cm.s^{-1}$, field of view = 160mm, matrix = 48 x 64, slice thickness = 6 mm.

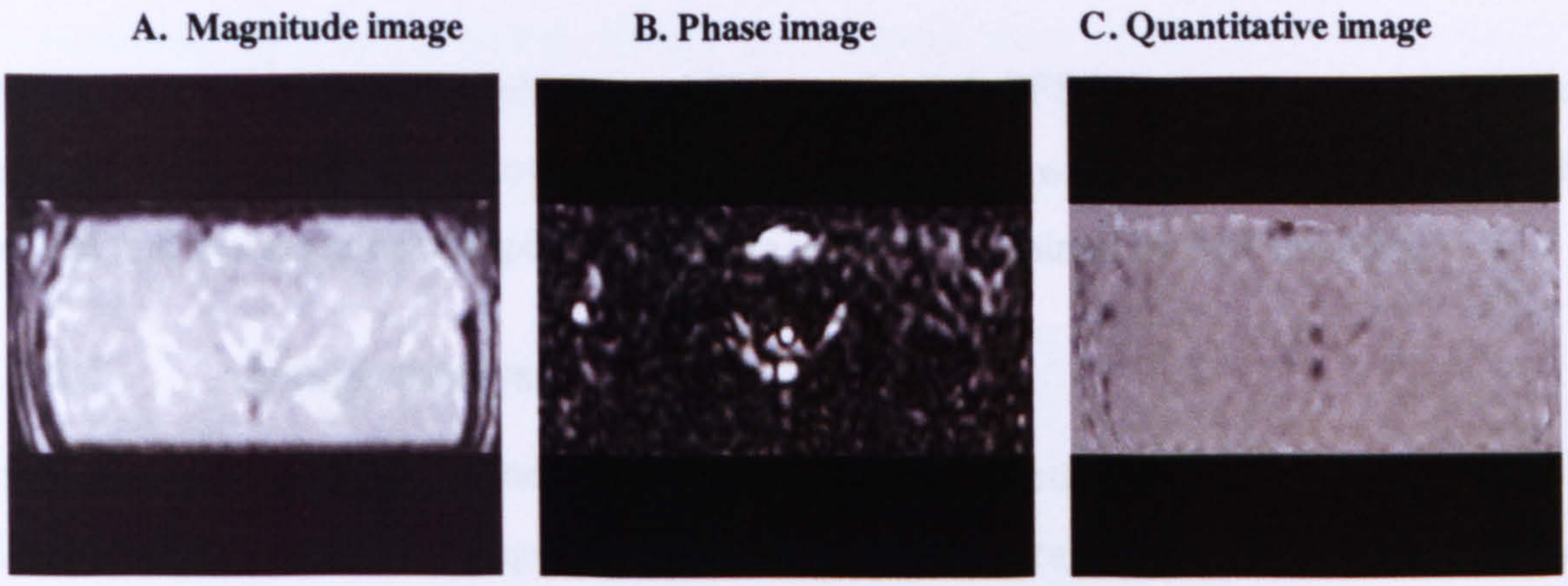



**Figure 45 Cerebral aqueduct PC image.**

The magnitude image (A) shows the anatomical detail of the ROI, in this case a section between the 3rd and 4th ventricles, just anterior to the cerebellum and postero-superior to the pons (see Fig. 32). The phase image (B) shows the presence of flow in the aqueduct which is the brightest circular structure at the centre of the image (the other hyperintensities are blood vessels). In the quantitive image (C) the flow of cerebrospinal fluid is actually measured.

#### 3.3.4.3.7 Foramen Magnum PC

The flow of CSF was also examined at the foramen magnum. An axial sequence perpendicular to the spinal canal at the level of C2 was carried out with the cardiac frequency yet again altered in motion using peripheral gating.

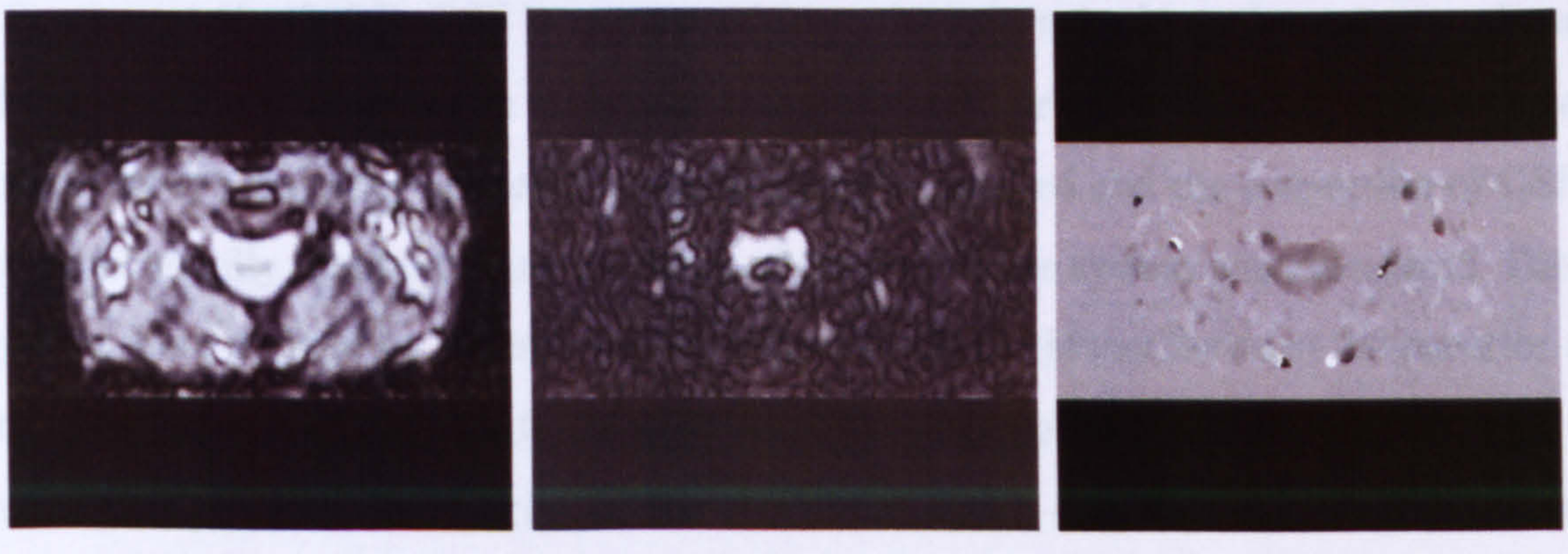



**Figure 46 Foramen magnum PC image**

The magnitude image (A) shows the anatomical detail of the ROI, in this case a section perpendicular to the spinal canal at the level of C2. The phase image (B) shows the presence of flow in the spinal canal which is the large bright structure at the centre of the image. In the quantitive image (C) the flow of cerebrospinal fluid is actually measured.

This is one the most comprehensive MRI studies of CFS/ME ever to be undertaken. Cerebral blood flow, CSF flow and volume changes, possible cerebral pathology plus cervical and thoracic duct lymphatic drainage were all examined by MR scanning.

### 3.3.4.4 Image analysis

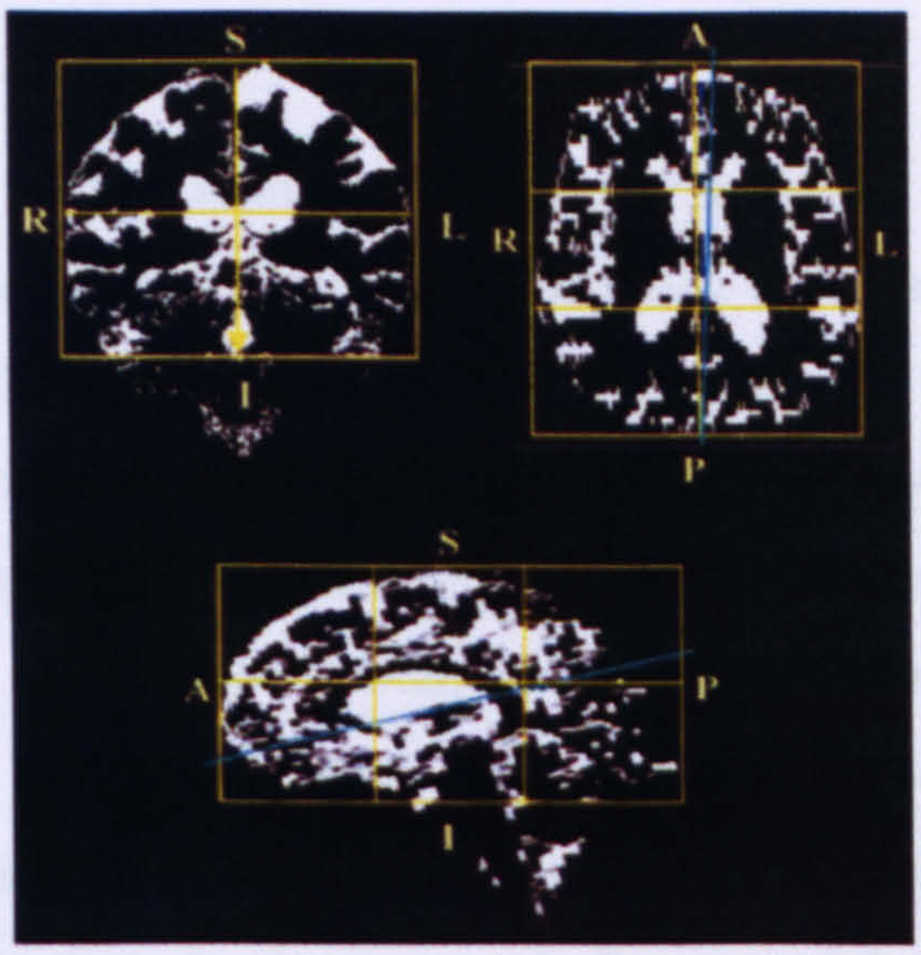
Image analysis took place in the Neuro Image Analysis Centre (NIAC) in the University of Manchester Division of Imaging Science and Biomedical Engineering. Analysis was performed using the software tool (TINA) which has been developed locally to support neuroimaging analysis of tasks of this type. Morphological image analysis consisted of segmentation of grey matter, white matter, CSF and high signal lesions which are identified in the images. These were be assigned probabilistic values using a Bayesian probability cluster analysis technique. These probabilistic complex data maps were used to extract lobar and regional tissue volumes for direct comparison between control and experimental groups. High resolution imaging of cervical and upper lymph nodes was performed at the same examination.

#### 3.3.4.4.1 Cerebral atrophy

The degree and distribution of cerebral atrophy were analysed using the method described by Thacker *et al.*, (2002). CSF is segmented from the spin-echo inversion-recovery images and the resultant CSF image is registered into a standard orientation. A coordinate system, bounded by the extremes of the CSF space, was then applied and the proportion of CSF in each of 12 equally sized arbitrary divisions of the coordinate system was calculated. The 12 segments were defined by the mid-sagittal plane, a plane midway between the superior and inferior boundaries of the coordinate space and two planes placed equidistantly between the anterior and posterior boundaries of the coordinate space (see Fig. 47). This produced a measure of CSF volume and distribution normalised for head size and scaling errors.

CSF voxels representing the lateral ventricles were manually selected from the binary images for volumetric measurement of the lateral ventricles. The segmented ventricle images were manually checked by 3D volume rendering to ensure that voxels extraneous to

the ventricles were not included. If any such voxels were present they were manually removed. The measured ventricle volume was again normalised to the dimensions of the coordinate system enclosing the CSF space to correct for variations in head size.




**A = Anterior**
**P = Posterior**
**S = Superior**
**I = Inferior**
**R = Right**
**L = Left**

**Figure 47 Fast spin echo inversion-recovery images showing position of bounding box in coronal, transverse and sagittal planes (Thacker *et al*., 2002)**

The brain was divided into 12 equal boxes. The blue line in the transverse (top right) and sagittal (bottom) represent the original baseline of the image before being adjusted to fit into the collective bounding box. No rotation was required in the coronal plane (top left).

In addition data was spatially normalised and registered into a standard Taliarach co-ordinate system to allow statistical comparison of grey matter and white matter density functions. This technique allowed automated non-biased identification of areas of focal atrophy with low spatial frequency which may be occurring within the data sets.

#### 3.3.4.4.2 Deep white matter hyperintensities

White matter lesions were identified on heavily T2 weighted optimised FLAIR images and scoring was done blind and subjectively. Scoring was performed by an experienced neuroradiologist using a scoring system extensively tested and published by staff of the Neuroimaging Centre in Manchester (Scheltens *et al*., 1993).

Diffusion tensor images were used to calculate mean diffusional tensors, apparent diffusional coefficients and regional fractional anisotropy measurements and to produce parametric images of each of these parameters. Images were then examined for statistical

outlyers based on normal values extracted from the data distribution in order to identify the possibility of white matter lesions.

### 3.3.4.5 Imaging of the lymphatics

#### 3.3.4.5.1 The thoracic duct

Visualisation of the thoracic duct by MR scanning is normally achieved using a contrast agent which would have raised health and safety issues. However a first scanning method was reported when Hayashi and Mityazaki used a short echo spacing 3D half-fourier, fast spin-echo sequence without a contrast agent and produced coronal and sagittal MIP (maximum intensity projection) images of the duct (Hayashi and Mityazaki, 1999). This method was not possible utilising the scanner at Manchester. At its abdominal origin the thoracic duct is only 0.5 to 2mm in diameter, however it was possible to visualise axial images of the lower part of the thoracic duct at the L2 level utilising the earlier protocol discussed in 3.3.4.5.2 but only when there is a large enough diameter of the duct lumen.

Although general opinion is that the cisterna chyli is usual found at the L1-L2 level (see Fig. 48), it has been shown that the cistern is more of an anomaly than the norm and that there are many variations of the origin of the duct (Anson, 1963). In a recent study the cisterna, when present was found to be more in the L3-L4 segment (Lee and Cassar-Pullicino, 2000). The first area to be scanned was thus the lower end of the thoracic duct anterior to the L2 /L3 segment.

The subject lay supine on the table on synergy spine coil, centred at L2. A wedge was placed under their knees for added comfort and an initial survey took place using a T1 weighted series including the ROI from the base of L3 to the top of L2 (see Fig. 49).

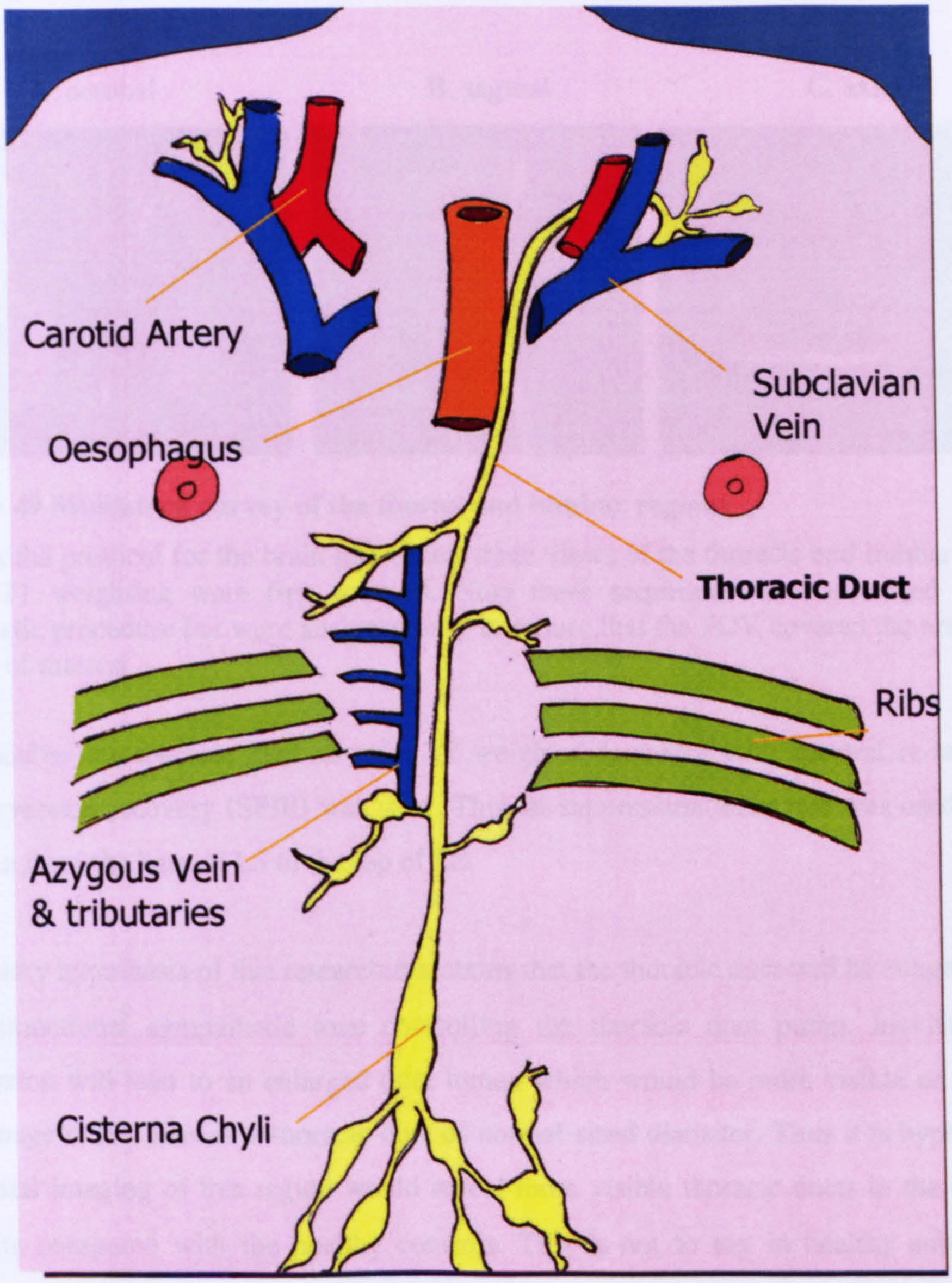



**Figure 48 The Thoracic Duct**

The thoracic ducts abdominal origin is usually at L1-L2 but may be lower. The enlarged cisterna chyli is not always present. The duct begins on the right side of the abdomen and passes across to the left side at the nipple line and ends at the left subclavian vein

Patient Preparation:

#### 3.3.4.5.2 Multistack MST survey.

This sequence was a T1 weighted series of scans in three different planes.

A. coronal B. sagittal C. axial

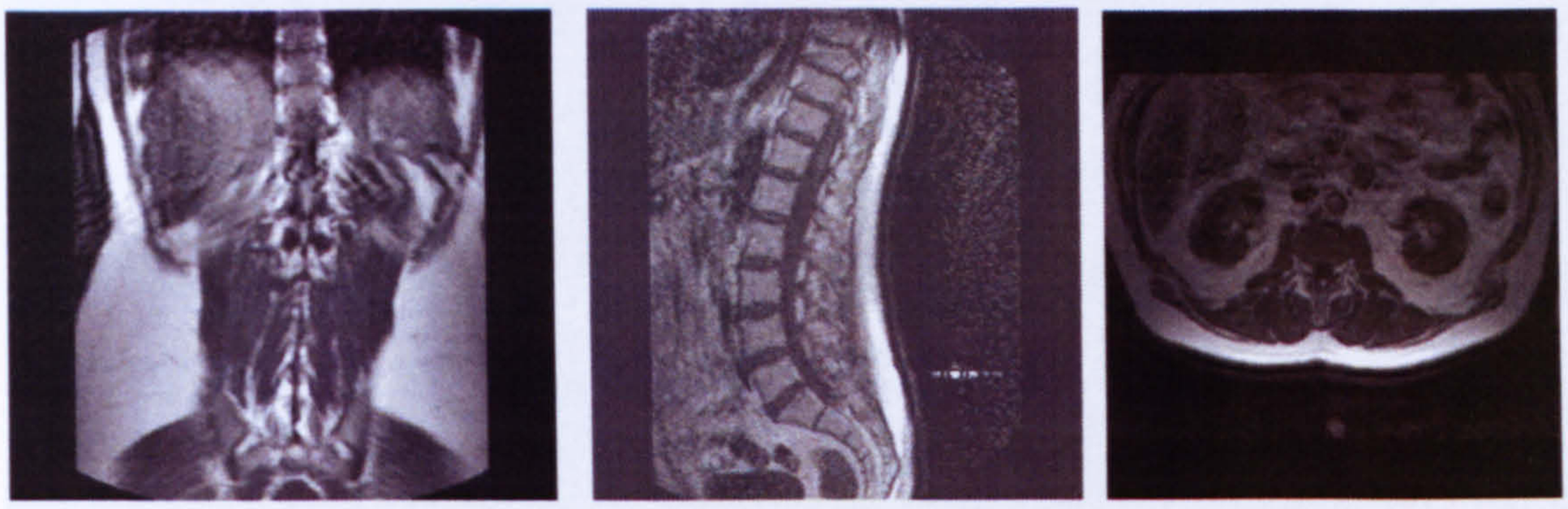


**Figure 49 Multistack survey of the thorax and lumbar regions**

As was the protocol for the brain sequences, three views of the thoracic and lumbar regions using T1 weighting were first scanned. Note these sequences were not used for any diagnostic procedure but were analysed only to ensure that the FOV covered the area of the region of interest.

To visualise the thoracic duct an axial T2 weighted sequence with spectral re-saturation with inversion recovery (SPIR) was used. This fat suppression technique was used to scan the area from the base of L3 to the top of L2.

A primary hypothesis of this research maintains that the thoracic duct will be congested due to dysfunctional sympathetic tone controlling the thoracic duct pump. Inevitably this congestion will lead to an enlarged duct lumen which would be more visible on an axial MR image than a scan of a thoracic duct of normal sized diameter. Thus it is hypothesised that axial imaging of this region would reveal more visible thoracic ducts in the CFS/ME subjects compared with the healthy controls. This is not to say in healthy subjects the thoracic duct is not apparent. What is suggested is that a higher proportion of visible ducts should appear on images of the CFS/ME sufferers. The Null hypothesis would be achieved if there appeared an equal proportion of visible thoracic ducts in both the CFS/ME groups and the healthy control group. The thoracic duct was scanned at its lower origin at the L2/L3 segment. The sequence was T2 weighted to illustrate lymph-engorgement in thoracic duct viewed in an axial image with the thoracic duct lying posterior and slightly left of the

aorta anterior of the vertebral column (see Fig. 58). Below is a simple T1 weighted axial image of the region of interest showing the anatomical detail before the SPIR technique was employed.

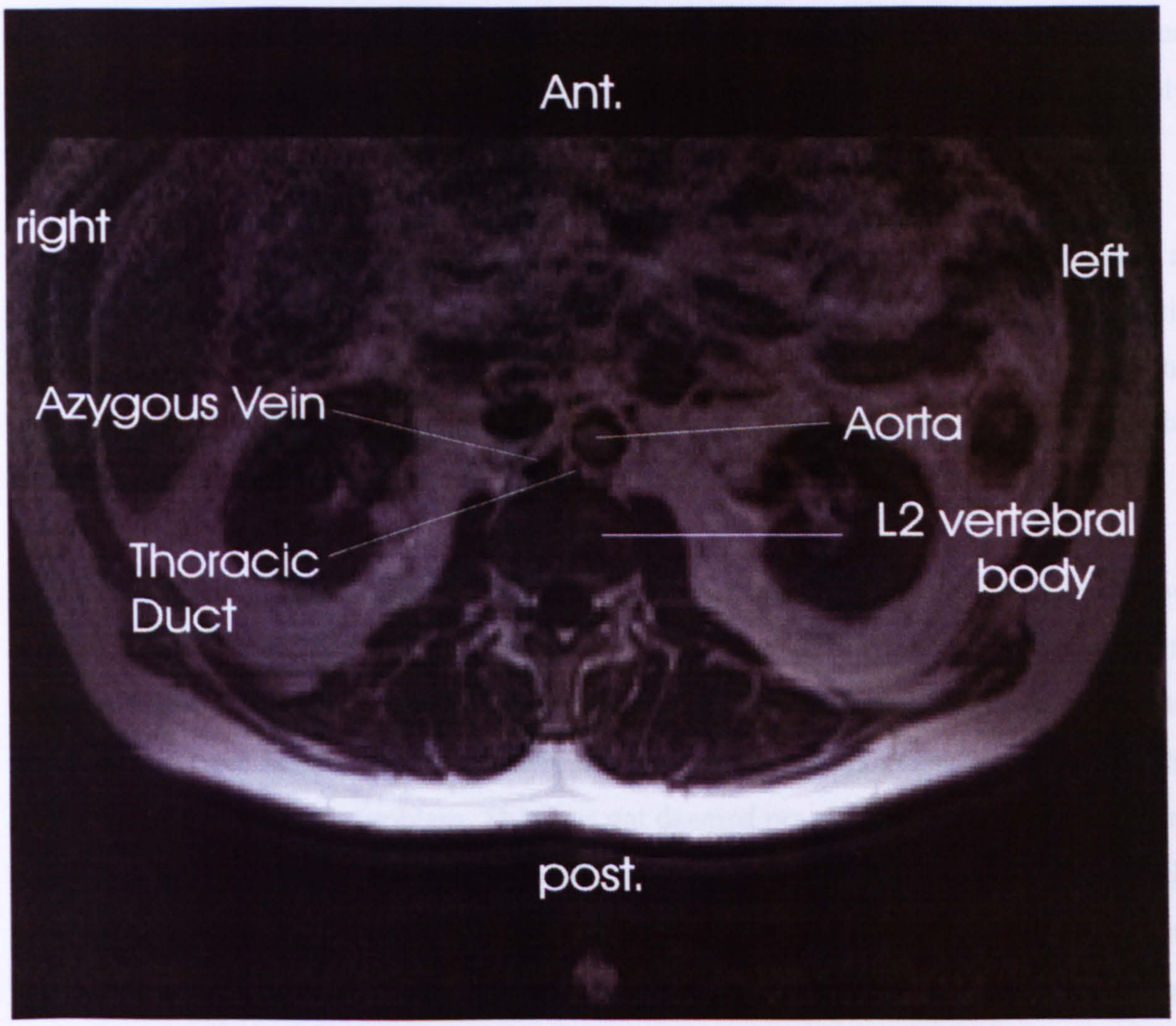



**Figure 50 T1 weighted scan of L2 segment of the thoracic duct**

This is a magnified image of the axial scans taken in the survey (Fig 49 C) Even though this image was not intended to show detailed anatomy it is still possible to see the thoracic duct lying posteriorly and just right of the aorta.

#### 3.3.4.5.3 The Cervical Lymph

The revised CDC criteria for CFS/ME (Fekuda *et al.*, 1998) include slightly enlarged cervical and axillary lymph nodes as a physical diagnostic sign. Clinical findings by the author have also revealed palpable superficial swollen thoracic and cervical lymphatics in all CFS/ME patients. Enlarged lymph vessels are usually most noted in the breast tissue with accompanied tenderness and occasional mastitis. The left breast is the more commonly affected.

As has already been stated the thoracic duct which in the upper thorax is left sided is controlled by sympathetic nerves. If the duct is not pumping sufficiently due to sympathetic dysfunction or an erroneous reflux mechanism pumped the chyle back into the tissues the first signs of blockage would probably arise in the neck and chest. This would explain the aforementioned swollen tissue.

Lymphatics contain unidirectional valves which may be damaged if the normal flow became retrograde or congested. This would create engorged lymph vessels similar to varicose veins. It was originally planned to scan an enlarged lymph vessel in the breast which would have been easier to identify and not being next to major blood vessels the artefact would be less of a problem. This was not deemed practical as the scan sequence for breast lymphatics requires the patient to lie prone on an uncomfortable coil. This would have aggravated breast pain felt by most of the CFS/ME patients in the study. Examining the cervical lymph nodes was deemed less intrusive and the scanning was more comfortable for the subjects, although during this 3 minute sequence subjects had to avoid swallowing.

The cervical scans were often marred by artefact from the carotid artery lying close by the coil. An enlarged lymph node adjacent to the anterior margin of the sterno-cleidomastoid was most commonly chosen (see Fig. 53). The choice of node to be examined was determined on two factors a: it was the most palpable, and b: it lay as far as possible away from the major arteries.

The treatment involved manual lymphatic drainage of the cervical region and so the size of lymph nodes may be reduced with a year of therapy. However if there has been a reflux of lymph for a long period prior to the treatment the valves may be permanently damaged which would mean that the disease could only be helped by improving the drainage of toxins but the lymphatic vessels would always be prone to engorgement.

Patient Preparation:

1. A cervical lymph node was identified by palpation and marked with pen.
2. The patient was repositioned to scan the cervical region and the surface coil was positioned over the marked lymph node.
3. A multistack survey was employed using a synergy coil, also known as a spine coil and then repeated using a C4 coil (See Figs. 51 and 52).

A: Sagittal B: Coronal C: Axial

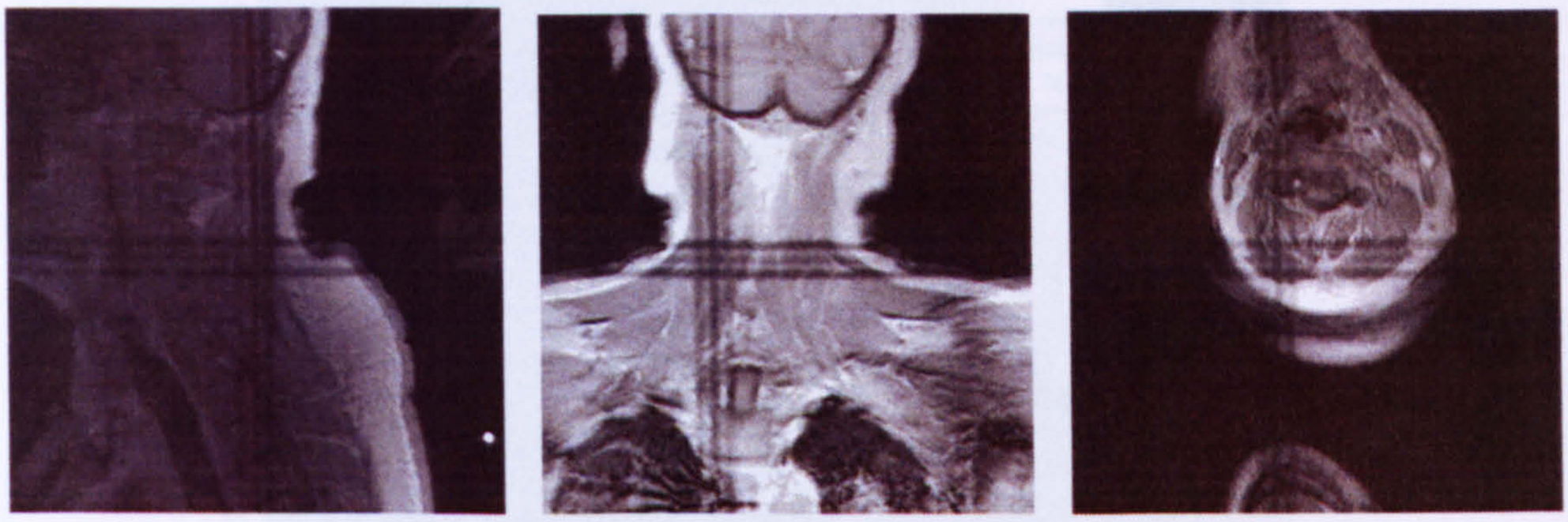


**Figure 51 Multistack image of cervical region**

The cross lines guided the radiographer to the exact ROI which was determined before the scan by the author after palpating the cervical region for a suitably enlarged lymph node.

The cervical scans were prepared using a surface coil positioned in the anterior part of the neck adjacent to the border of the sternocleidomastoid. Note the disturbance in the images due to artefact (see Fig. 51C).


**Figure 52 Artefact in cervical lymph scans**

There was a good probability that artefact would affect the clarity of the cervical images as is seen in the axial scan C. This is due to the signal disturbance from breathing and affects from the strong pulsations in the cervical arteries. The patient was instructed not to swallow during these sequences to reduce a further source of artefact.

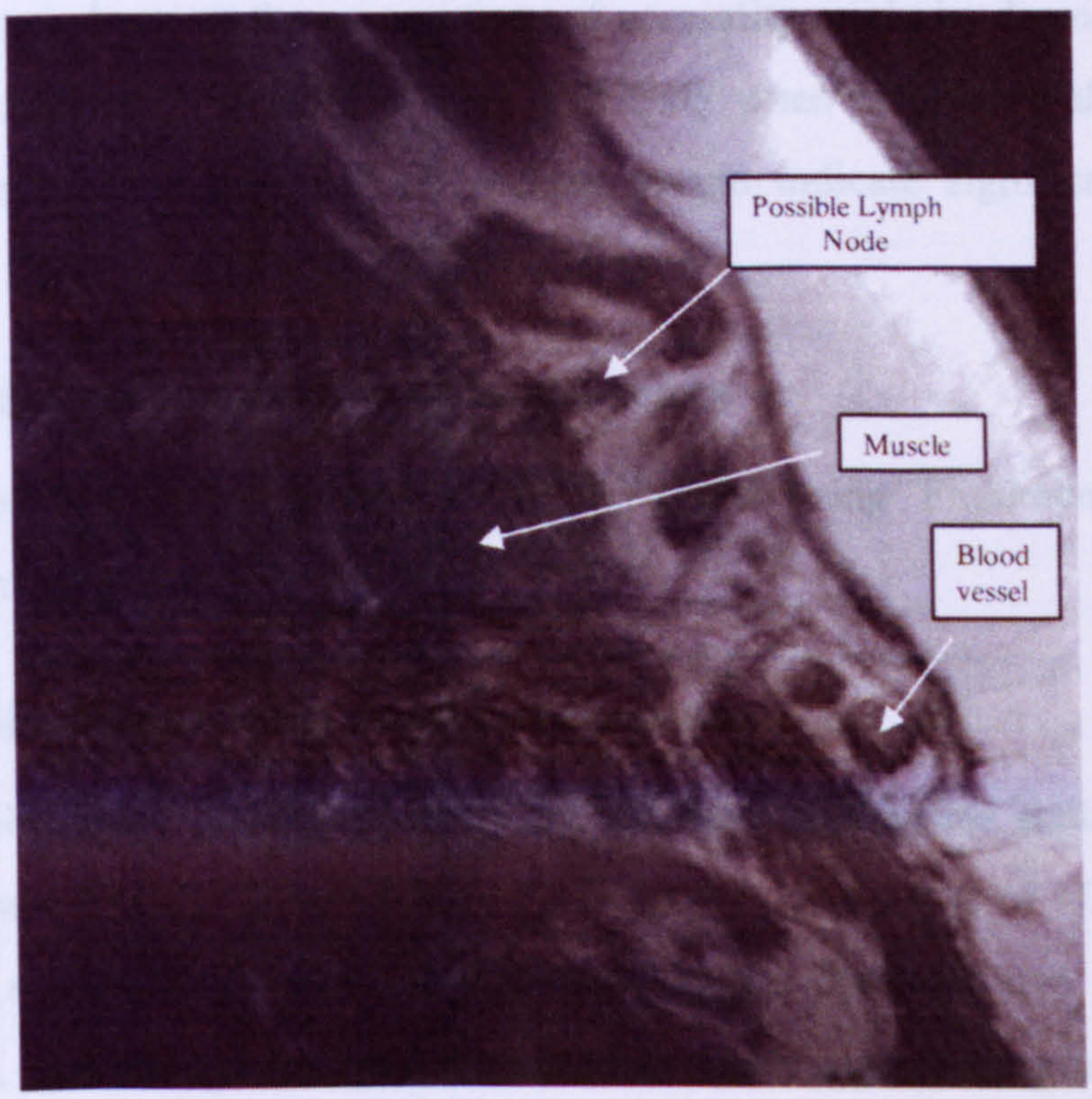



**Figure 53 Sternomastoid and cervical lymph node**

Sagittal section showing magnified subcutaneous structures in anterolateral region of cervical soft tissue. Note the similarity between blood vessel and lymph node making identification extremely difficult.

As with the other radiological examinations, all the scans of the thoracic and cervical lymphatics were conducted by Professor Alan Jackson, the consultant neuroradiologist heading the project's Manchester University MR Scan team. To reduce bias the images were viewed blind in that Prof. Jackson was unaware which group the subjects belonged to.

## 3.3.5 Statistical analysis

### 3.3.5.1 Statistical analysis of symptomatology

Statistical analysis of the outcome of the patient group compared with the controls was carried out. Kruskal-Wallis nonparametric one-way analysis of variance was used to test for significant differences in questionnaire responses, as percentages of maximum scores possible, between the three treatment groups. This especially in view of the small number in the groups, nonparametric tests were used rather than parametric one-way and two-way analyses of variance, because the assumptions of normality might be deemed inappropriate for percentage changes. A p-value of less than 0.05 when examining the difference of questionnaire results over the year of research would indicate significant reduction in symptoms.

### 3.3.5.2 Statistical analysis of brain scans

Comparisons between the 3 groups were performed using Freidman's ANOVA for nonparametric matched sets.

### 3.3.5.3 Statistical analysis of lymph scans

Due to the small number of subjects analysed, the most appropriate statistical test on the thoracic duct scans was the 2- sided Fisher's Exact test. A p-value of $<0.05$ would mean that there was a statistically relevant difference in the diameter size of thoracic duct between groups. Not enough data was collected to make any meaningful analysis on the cervical lymph scans (see 3.4.4).

## 3.4 Results

### 3.4.1 Results of symptom analysis

The scores of the self report questionnaires were calculated and the differences between the mean percentage scores at the beginning and end of phase 2 were tabulated (see Table 14). The changes in symptom score in the treated group was compared with the control groups and subjected to statistical analysis.

| Questionnaire | Treated Group % improved | Non-Treated Group % improved | Normal Control Group % improved |
|---|---|---|---|
| Health | 16.63 | -1.99 | 0.14 |
| Back Pain | 29.39 | 2.47 | 0.92 |
| Depression | 8.86 | -1.24 | 0.17 |
| Anxiety | 8.64 | 2.83 | -0.8 |
| Sleep | 9.74 | -1.39 | 0.98 |
| Cognition | 19 | -9.45 | -6.11 |
| Nott. Health | 15.42 | 2.92 | 1.37 |
| PFRS | 23.74 | -5.82 | -0.93 |

**Table 14 Mean percentage change in symptom questionnaires (Phase 2 results)**

The values listed above are the differences between the mean percentage scores at the beginning and end of phase 2, where 0% = symptom free and 100% was maximum severity possible. The improvement in the treated group compared with the control groups is seen in the higher scores in the 2nd column. Note that a –ve value = a worsening in the symptoms over the year.

Due to the smaller numbers involved in phase 2 compared with phase 1, different statistical tests were conducted. This time the Kruskal-Wallis nonparametric one-way analysis of variance was used to test for significant differences in questionnaire responses, as percentages of maximum scores possible, between the three treatment groups (See Appendix A10).

Table 14 lists the scores obtained for the symptom questionnaires, expressed in overall mean percentage change relative to the maximum score possible. A p-value less than 0.05 indicates significance at the 5% level. For all eight questionnaires the estimated median increase was greatest in the treatment (RV) group.

Significant reductions in most symptoms, notably fatigue (PFRS), pain and cognitive function were reported to result from treatment of the CFS/ME group. However the symptoms of depression, anxiety and symptoms such as insomnia were not significantly reduced following treatment.

The p-values of the statistical tests are listed below:

**Health versus Group** **p= 0.009 (adjusted for ties)**

**Back Pain versus Group** **p = 0.002 (adjusted for ties)**

**Depression versus Group** **p= 0.057 (adjusted for ties)**

**Anxiety versus Group** **p = 0.507 (adjusted for ties)**

**Sleep versus Group** **p= 0.069 (adjusted for ties)**

**Cognition versus Group** **p = 0.019 (adjusted for ties)**

**Nott Health versus Group** **p = 0.263 (adjusted for ties)**

**PFRS versus Group** **p= 0.007 (adjusted for ties)**

## 3.4.2 Results of brain scan analysis

### 3.4.2.1 Ventricular volume

The present study examined both the volume of all the CSF within the skull vault of the prosencephalon and the volume of CSF within the lateral ventricles. Early on in this second phase of the study ventricular volume was observed visually to be increased in some of the CFS/ME group compared with the matched control (see Fig. 54). However statistical analysis would show if there was a significant increase in the patient group as a whole compared with the healthy controls.

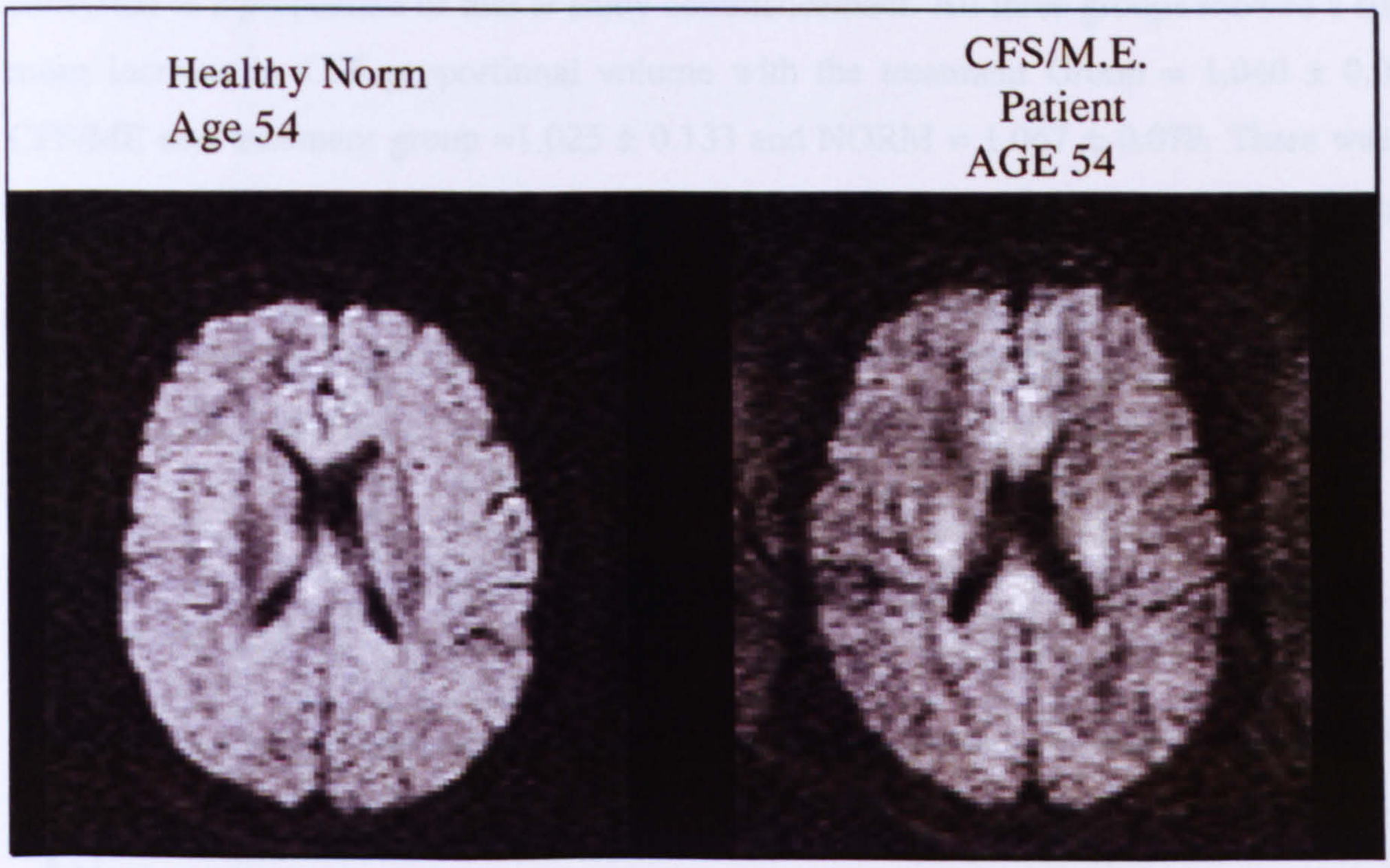



**Figure 54 Observable ventricular volume increase in a CFS/ME patient**

The two axial scans above were taken from equivalent slices of a CFS/ME patient and an age, gender and weight matched control; the wider lateral ventricles on the right image indicate a greater ventricular volume in CFS/ME.

In the present study measurements of proportionate CSF volume made from scans obtained 90 minutes apart were very similar. The 2nd measurement converted to a proportion of the first a mean value of 0.9976± 0.0505 was calculated for all 27 subjects, showing good

reproducibility for the technique in the short term. Comparison of the proportionate CSF volume between the 3 subject groups at the beginning of the study showed no significant difference between either of the CFS/ME patient groups or the control group (Freidman's ANOVA, $P$=0.339). See appendix A11 for full data.

As described in 3.3.4.4.1 cerebral atrophy was analysed using a coordinate system, bounded by the extremes of the CSF space. This consisted of 12 equally sized arbitrary divisions of a larger 'bounding box' which produced a measure of CSF volume and distribution normalised for head size and scaling errors. To assess and compare longitudinal changes in CSF volume, the proportion of CSF in the total bounding box after 1 year was converted to a proportion of that at study commencement. All three groups showed a slight mean increase in CSF proportional volume with the treatment Group = 1.040 ± 0.061; CFS/ME non treatment group =1.025 ± 0.133 and NORM = 1.067 ± 0.078. There was no significant difference in change between the control and patient (including successful treatment) groups ($P$ = 0.73).

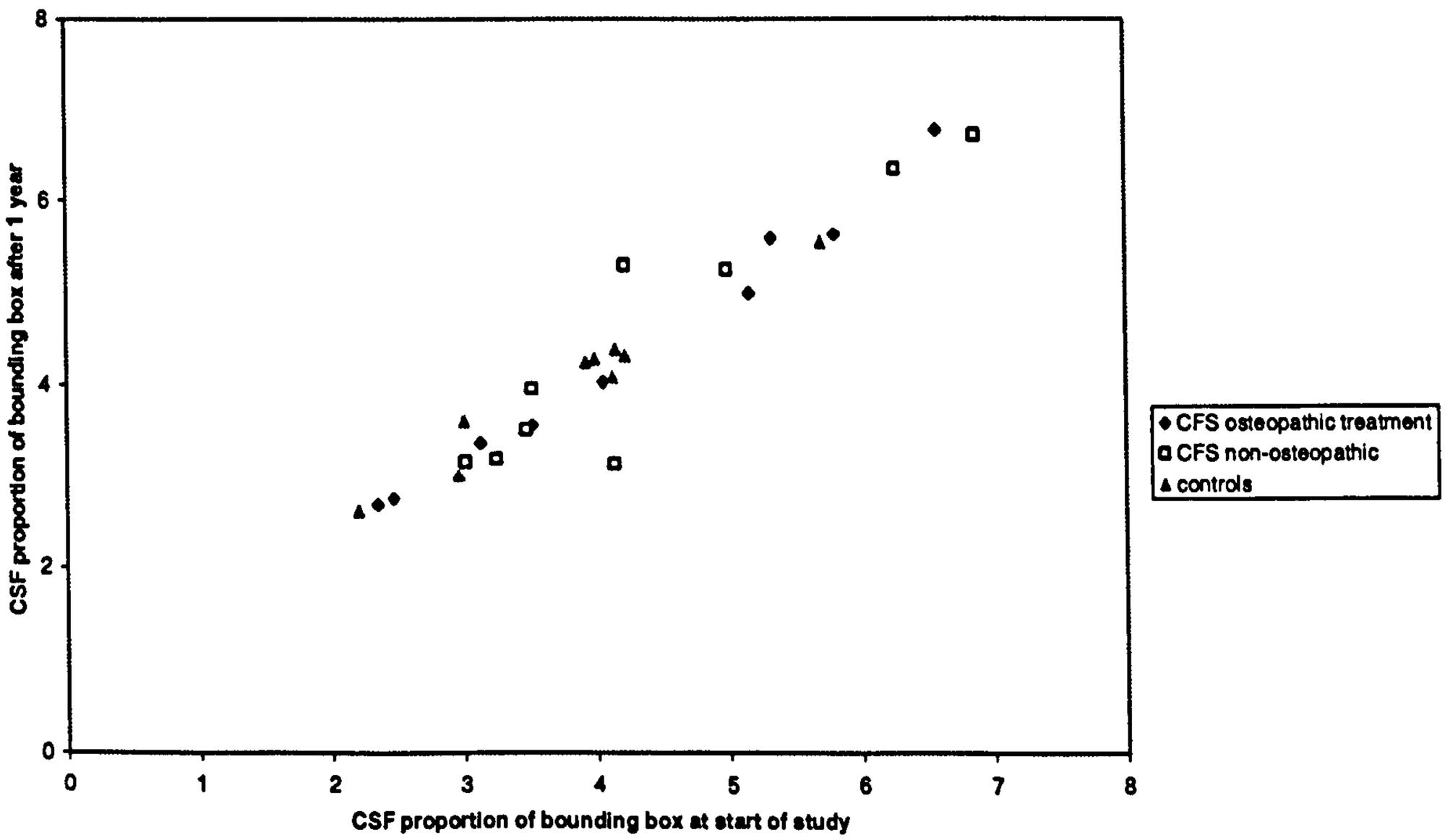



**Figure 55 Cerebrospinal fluid proportional volume**

The scattergram of CSF proportional volume compared with the overall volume in the bounding box, expressed as a percentage, after one year against volume at study commencement.

Figure 55. shows CSF proportional volume after 1 year against volume at study commencement. It suggests no significant difference between any of the groups and no significant inter-group differences in the change over the course of 1 year. It is interesting however, that the 2 outliers were both non-treated CFS/ME patients with one showing a large reduction in proportional volume and the other a substantial increase for no apparent reason.

Comparison of ventricular volume at commencement of the study showed no significant differences between the 3 groups ($p = 0.339$) and no significant inter-group differences in the change over the course of 1 year ($p = 0.733$).

### 3.4.2.2 Deep white matter hyperintensities

The table format portrayed in Scan Table 1 was employed to enumerate the amount of noticeable deep white matter hyperintensities found in the different sections of the brain. There are four levels of lesions which may produce differing sizes and brightness of the hyperintensities depending on the cause of pathological changes occurring in the white matter.

The score of A, B, C or D were given if pathological lesions were seen with D being most serious pathological change. No letter score was recorded if the hyperintesity was not of any significant size or brightness. A numerical score was given for the number of minor sub-clinical hyperintensities seen. These lesions are too small to be caused by any pathology and occur naturally in brain tissue due to the ageing or other physiological processes. The presence of any periventricular hyperintensity was also noted. This finding may indicate pathology of the ventricular surface.

## SCAN TABLE 1.

DEEP WHITE MATTER HYPERINTENSITIES

| Code no:<br>Scan no:<br>Time: | Left | Right |
|---|---|---|
| Frontal | | |
| Parietal | | |
| Occipital | | |
| Temporal | | |
| TOTAL BRAIN | | |

**Periventricular hyperintensity (PVH) □**

**Figure 56 Chart used to tabulate occurrence of DWMH and PVH**

This chart was used by the consultant radiologist when examining the FLAIR scans of the brain to determine if and how many deep white matter hyperintensities were present (see Fig. 41). The presence of periventricular hyperintensities was also investigated as they are also a sign of pathology within the brain.

The results from this part of the radiological investigation are tabulated below (see Tables 15-17).

| Code number | T2 left frontal | T2 left parietal | T2 left occipital | T2 left temporal | T2 right frontal | T2 right Parietal | T2 right Occipital | T2 right temporal | PVH |
|---|---|---|---|---|---|---|---|---|---|
| Rv01 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Rv03 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Rv04 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Rv05 | 0 | 3 | 0 | 3 | 0 | 0 | 0 | 0 | 0 |
| Rv06 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Rv06 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| Rv07 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Rv08 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Rv09 | 0 | 1 | 0 | 3 | 0 | 0 | 0 | 0 | 0 |
| Rv10 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

**Table 15 DWMH reported in the treated patient group (left and right)**

| Code number | T2 left frontal | T2 left Parietal | T2 left occipital | T2 left Temporal | T2 right frontal | T2 right parietal | T2 right Occipital | T2 right temporal | PVH |
|---|---|---|---|---|---|---|---|---|---|
| Cp01 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| Cp02 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cp03 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cp04 | 3 | 2 | 3 | 1 | 2 | 3 | 3 | 1 | 2 |
| Cp05 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cp06 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cp07 | 3 | 1 | 3 | 1 | 2 | 1 | 0 | 0 | 1 |
| Cp08 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Cp09 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

**Table 16 DWMH reported in the untreated patient group (left and right)**

| Code number | T2 left frontal | T2 left Parietal | T2 left occipital | T2 left Temporal | T2 right frontal | T2 right Parietal | T2 right occipital | T2 right temporal | PVH |
|---|---|---|---|---|---|---|---|---|---|
| Nc01 | 0 | 2 | 0 | 2 | 3 | 3 | 1 | 2 | 0 |
| Nc02 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| Nc05 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Nc06 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Nc07 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Nc09 | 1 | 3 | 1 | 0 | 3 | 1 | 0 | 0 | 0 |
| Nco3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Nco4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Nco8 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |

**Table 17 DWMH reported in the healthy control group (left and right)**

All three groups showed low levels of WMH with no evidence of WMH in the basal ganglia or infratentorial structures in any patient. Mean scores were, for periventricular hyperintensity treated patients, 0.11 ± 0.33;untreated patients, 0.33 ± 0.71 and Norm, 0.11 ± 0.33 and for DWMH in the prosencephalon, treated patients, 1.55 ± 2.80;untreated patients, 1.67 ± 2.78 and NORM, 1.11 ± 1.45. There was no change in any of the summary (prosencephalic DWMH, basal ganglia hyperintensities and infratentorial hyperintensities) or individual component variables which make up the score between the baseline and 1 year follow-up scans. Since the Scheltens' scale presents summaries of the frequency of lesions it is possible that individual lesions may appear, resolve or change over time without a corresponding change in the resultant score. Direct comparison of baseline and 1 year follow up scans demonstrated new lesions in one subject (NORM, 3 lesions) and apparent resolution in two subjects (Norm, 1 lesion <3mm, untreated 1 lesion <3mm) (see appendix A11)

An example of the small discreet DMWH seen in this study is seen on the enlarged scan below (Fig. 57) showing two small white patches in the left temporal lobe (white arrows). The 53 yr old male CFS/ME sufferer (subject RV05) with two left temporal DWMH which may be age related in this case (Schmidt *et al.*, 1996). The patient RVO5, whose full medical history is recorded at the beginning of appendix A5, was the oldest of the treated group with very few hyperintensities being found in the other CFS/ME sufferers in the study.

The small punctate white matter hyperintensities seen in the image below (Fig. 57) greatly differ with scans seen when the hyperintensities are of definite pathological aetiology. The latter is seen in Fig. 42 showing an axial FLAIR image of a much younger patient with multiple sclerosis showing numerous large hyperintensities throughout the brain.

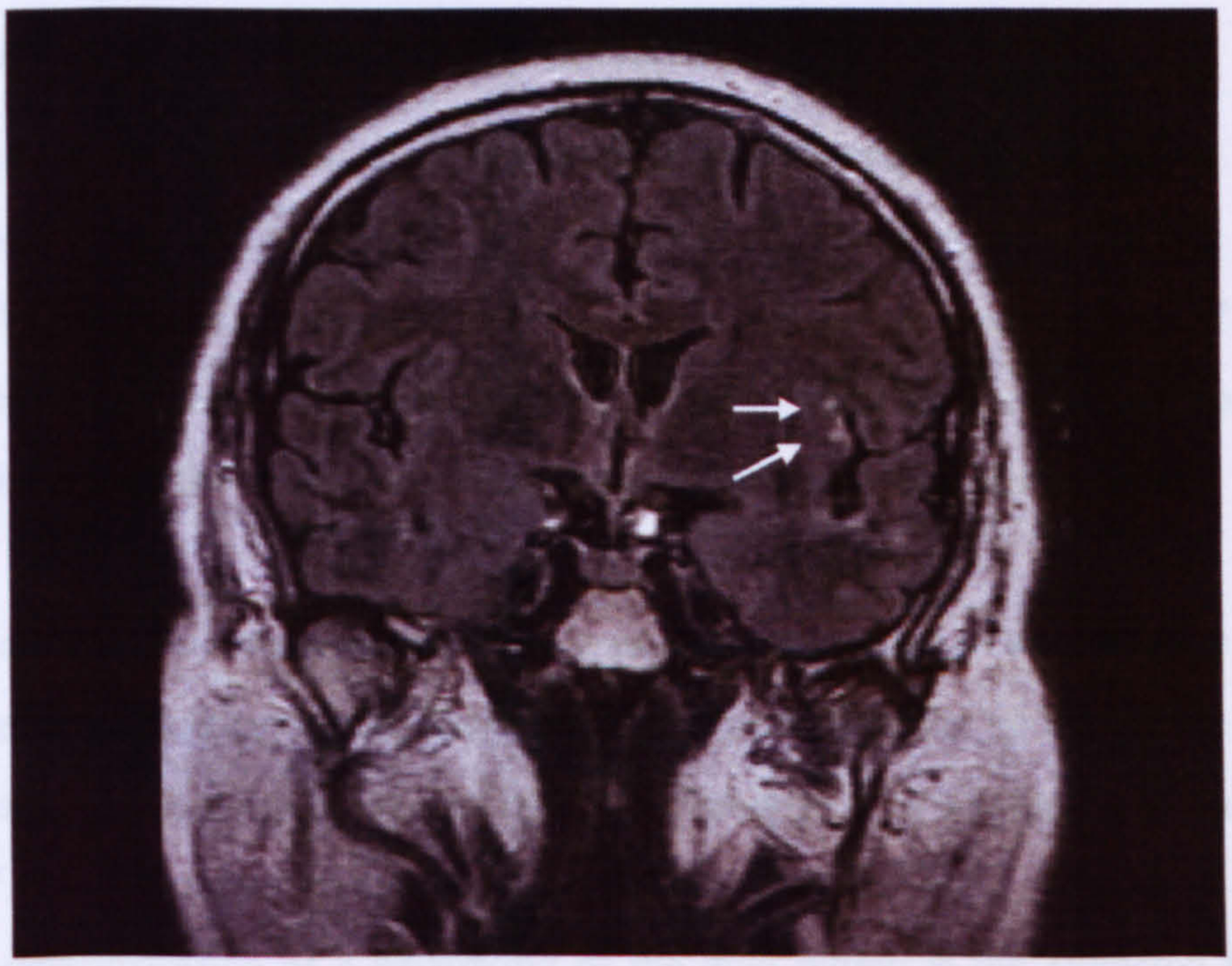


**Figure 57 Small discreet temporal lobe hyperintensities seen in coronal FLAIR image of subject RVO5**

Coronal FLAIR image of a 53 yr old male CFS/ME sufferer (subject RV05) with two left temporal DWMH which are most probably age related in this case (Schmidt *et al.*, 1996). The patient RVO5 was the oldest of the treated group with very few hyperintensities being found in the other CFS/ME sufferers in the study.

### 3.4.2.3 Blood and CSF flow

Analysis of cerebral blood flow data through the internal carotid and basilar arteries showed no significant differences when comparing change of mean flow over the year giving a p-value of 0.2273 which is much higher than the 0.05 needed to be of statistical significance. CSF flow data showed no significant differences in any of the inter-group comparisons with net flow difference of csf through the cerebral aqueduct giving a p-value of 0.71653 and a difference between the maximum flow p = 0.89484 (see Appendix A11). NB. The cerebral aqueduct is the region most sensitive to any change to CSF flow. If significant changes were found in the aqueduct sequences, further investigation into the flow through the foramen magnum would have taken place. In view of the insignificant changes in aqueduct flow it was decided that analysis of the larger flow in the foramen magnum was unnecessary.

## 3.4.3 Results of thoracic duct analysis

If there was less congestion in the thoracic duct after the year of treatment it would be of smaller diameter and a duller image compared with the original view. Below (Fig 58) are axial SPIR T2 weighted images showing the lower end of the thoracic duct of the research patient RV04 at the start of the project and a corresponding image matched for anatomical position at the end of the project demonstrating a possible effect of treatment.

The thoracic duct (TD) image brightness is much less intense in second scan indicating a possible sizeable reduction in the diameter. The lumen diameter of the thoracic duct of all subjects' scans was initially compared by the radiologist. The brightness of the image is an indicator of the amount of lymph fluid within the duct and thus a decrease in the signal intensity is demonstrative of a narrowing of the duct which is the expected finding when lymph engorgement has been reduced. Thus the hypothesis of central lymphatic engorgement as a major patho-physiological factor in CFS/ME would be supported if there was a reduction in the post-study signal intensity i.e. the post-treatment scan is smaller and/or duller than the pre-treatment scan.

BEFORE TREATMENT COMMENCED

AFTER YEAR OF TREATMENT

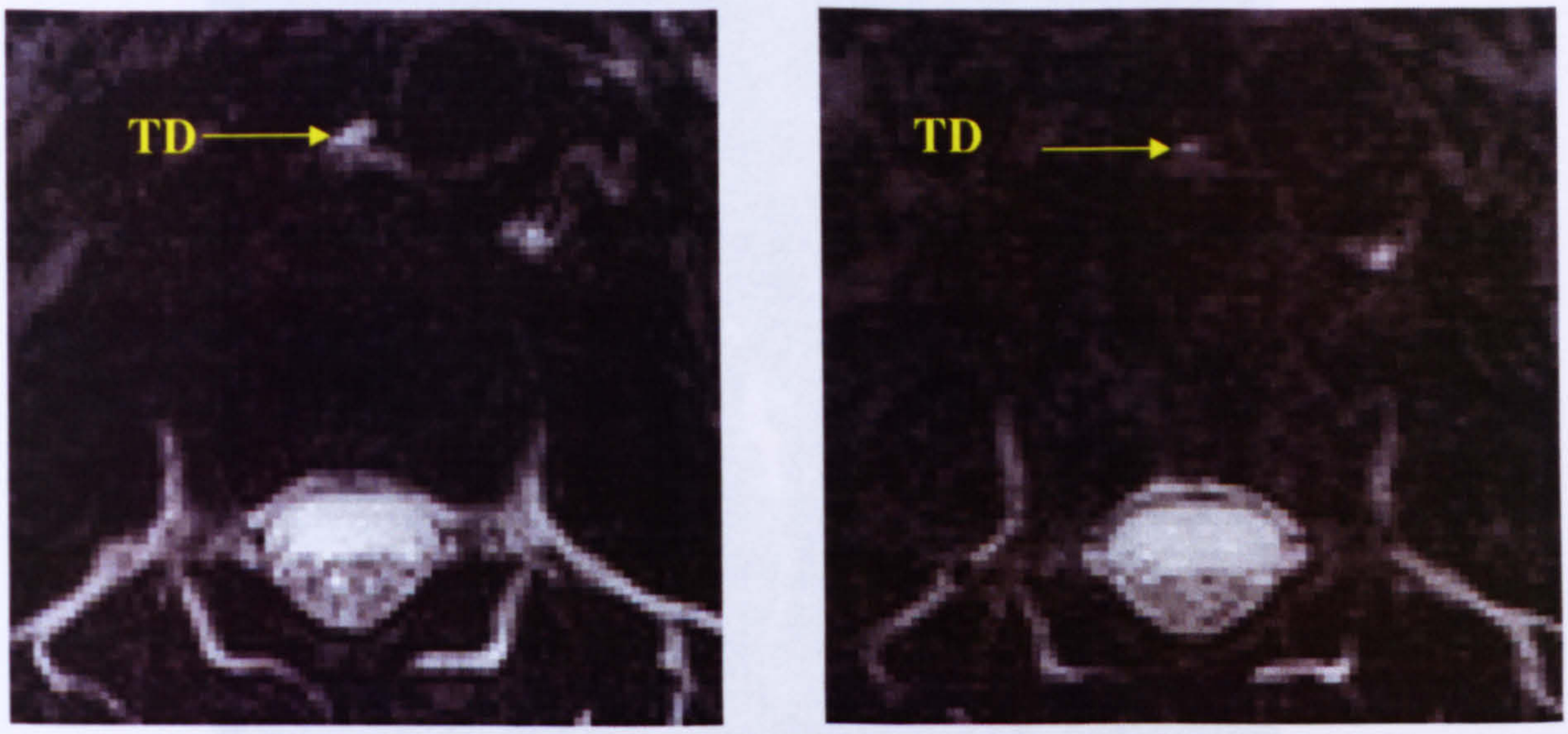



**Figure 58 Examining post-treatment diameter change of thoracic duct**

Axial scans of the thoracic duct of patient RV04 with a T2 weighting to show up fluid. TD= thoracic duct. In the first scan on the left the intense signal from the centre of the thoracic duct is due to the enlarged lumen filled with lymph fluid. The reduction in intensity and diameter size after treatment indicates a possible narrowing of the lumen with a reduction in any engorgement.

However when the difference was less noticeable this technique became increasingly complicated for the radiologist to identify the thoracic duct rather than the many veins in this region. Using a MIP image of the region solved this difficulty where a three dimensional model is created by the computer from the images in this sequence (Fig. 59).

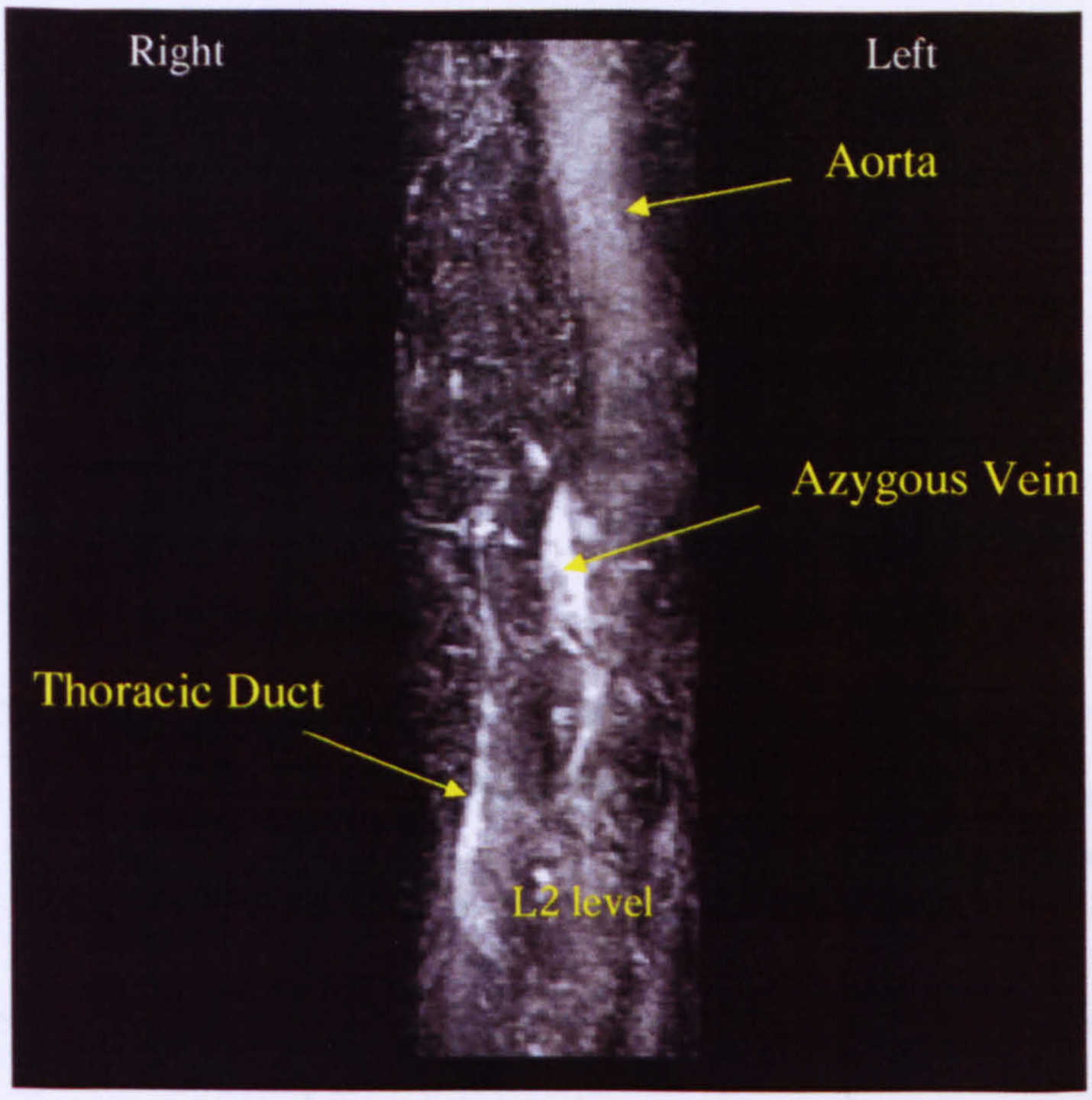



**Figure 59 MIP image showing the thoracic duct**

The MIP image concentrated on just the central area of the axial scan as shown in Fig. 48. A T2 weighted sequence with spectral re-saturation with inversion recovery (SPIR), a fat suppression technique, was used. The radiologist was able to rotate the image around the axis of the aorta and follow the path of the thoracic duct from L2 level up into the thorax, seen as the bright vessel, anatomically on right side, left on image.

The presence and diameter of a visible lower section of the thoracic duct at the L2/3 segment was recorded in Scan Table 2 which also noted whether the lateral aortic lymph nodes at this region were of significant size and number (see Fig. 60).

**SCAN TABLE 2.**

**NAME:** **DATE:**

| Code no:<br>Scan no:<br>Time: | Thoracic Duct | **Lateral aortic Lymph nodes.** |
|---|---|---|
| Visual | | |
| Diameter/ mm | | X |

**Figure 60 Table used to record state of deep thoracic lymphatics**

This chart was used by the consultant radiologist when examining the MIP scans of the upper lumbar region to determine if the thoracic duct was visible and how large the diameter.

In the first row a score of 1 was given if the thoracic duct was visible and 0 if the duct was too narrow to be seen. In the second row the diameter of the lumen of the thoracic duct was scored where 0 = < 2mm; 1 = 2-4mm and 2 = 4-6mm. The presence of a large mass of lateral aortic lymph nodes was also noted as this could also be evidence of lymphatic engorgement. The results from this part of the radiological investigation are recorded in Table 18.

| Code Number | T Duct Visible | Size |
|---|---|---|
| RV01 | 1 | 1 |
| RV03 | 1 | 1 |
| RV04 | 1 | 2 |
| RV05 | 1 | 2 |
| RV05 | Change to narrower duct following last treatment 1 | 1 |
| RV06 | 1 | 1 |
| RV07 | 0 | 0 |
| RV08 | 1 | 1 |
| RV09 | 1 | 1 |
| RV10 | 0 | 0 |
| CP01 | 0 | 0 |
| CP02 | 0 | 0 |
| CP03 | 1 | 2 |
| CP04 | 1 | 2 |
| CPO5 | 0 | 0 |
| CP06 | 1 | 1 |
| CP07 | 0 | 0 |
| CP08 | 0 | 0 |
| CP09 | 0 | 0 |
| NC01 | 0 | 0 |
| NC02 | 0 | 0 |
| NC03 | 0 | 0 |
| NC04 | 0 | 0 |
| NC05 | 1 | 1 |
| NC06 | 1 | 2 |
| NC07 | Seen in first scan at start of study 1 | 1 |
| NC07 | Not seen in final scan at end of year 0 | 0 |
| NC08 | 0 | 0 |
| NC09 | 0 | 0 |

**Table 18 Comparative study of dimensions of thoracic duct**

The table lists the scores taken from the data recoded on the Scan Table 2 following visual examination and scoring by the consultant radiologist. In the first column a score of 1 means that the thoracic duct was visible; 0 = duct too narrow to be seen. The second column shows the diameter of the lumen of the thoracic duct where 0 = < 2mm; 1 = 2-4mm and 2 = 4-6mm.

A summary and the significance of the results listed in Table 18 are tabulated below (tables 19, 20 and 21). Note that all 18 subjects suffering CFS/ME treated RV and control group CP members, were included in one group for this analysis as the amount of visible scans in these 18 subjects was a constant for the whole year.

| 1st scan | | | |
|---|---|---|---|
| | Number in Group | | |
| Group | | Visible on scan = 1 | Not seen on scan = 0 |
| CFS/ME | 18 | 10 | 8 |
| Norm | 9 | 3 | 6 |

**Table 19 Summary of thoracic duct visibility at start of phase 2**

Note that all 18 subjects who suffered from CFS/ME, treated RV and control group CP members, were regarded as one group only for the analysis recorded in this table and Table 20. This was due to the fact that the number of visible scans in all 18 subjects (CFS1 and CFS2) did not change after the year.

The data is graphically represented in the chart below (Fig. 61) comparing thoracic ducts seen in the first set of scans in the two groups expressed as a percentage of the total number in the group.

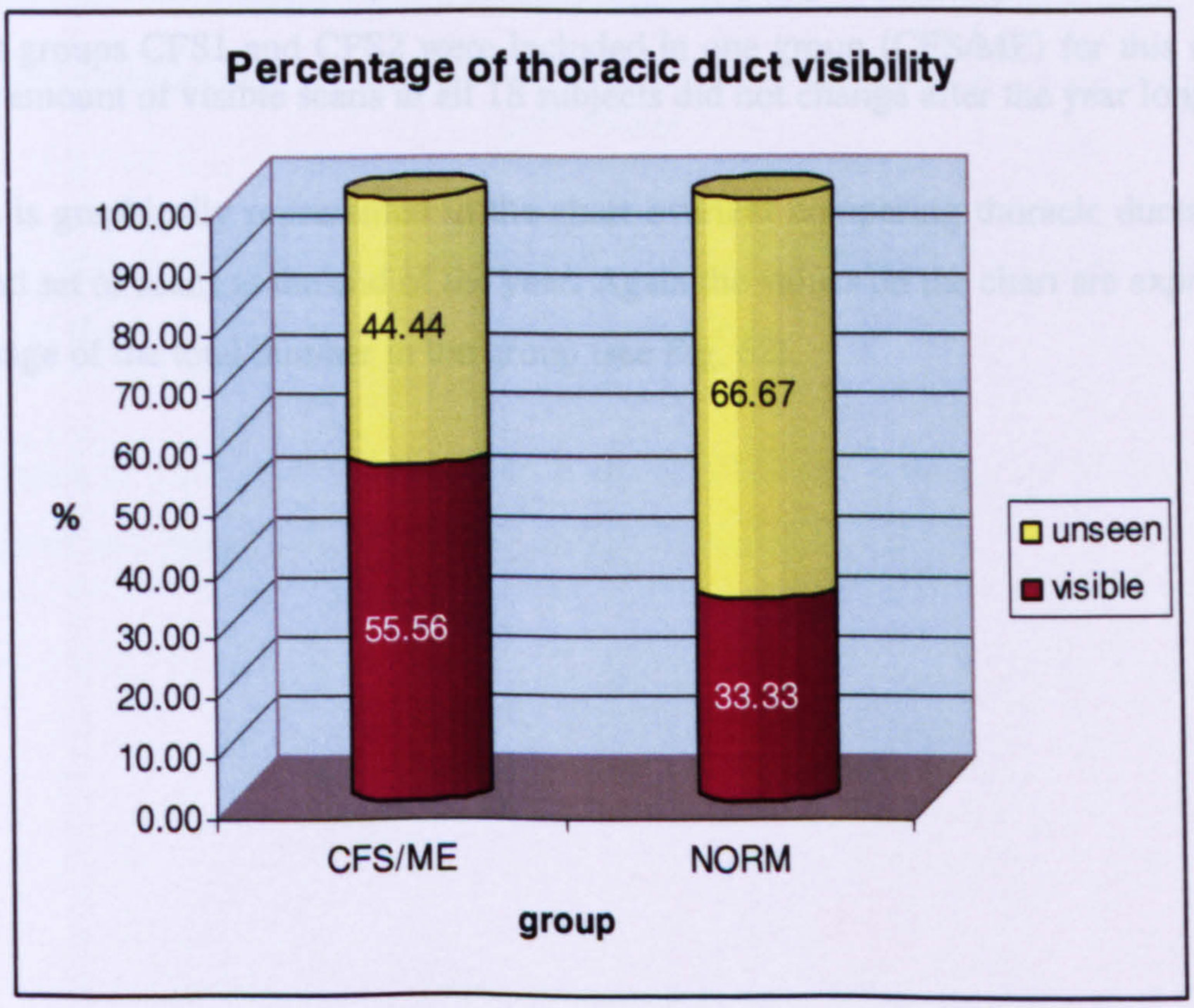



**Figure 61 Comparison of thoracic duct visibility at start of phase 2, expressed as a percentage**

The null hypothesis tested in this part was that there would be no statistically relevant difference between the visibility of the thoracic duct in the patient group and that of the healthy group. The p-value at the start of the second phase = 0.419 indicating no statistically relevant difference in diameter between groups.

A repeat set of scans was performed at the end of the year in phase 2 of this study with slight differences in the results compared with the findings in the initial scans.

| 2nd scan | | | |
|---|---|---|---|
| | Number in Group | | |
| Group | | Visible on scan = 1 | Not seen on scan = 0 |
| CFS/ME | 18 | 10 | 8 |
| Norm | 9 | 2 | 7 |

**Table 20 Summary of thoracic duct visibility at end of phase 2**

Note that groups CFS1 and CFS2 were included in one group (CFS/ME) for this analysis, since the amount of visible scans in all 18 subjects did not change after the year long study.

The data is graphically represented in the chart overleaf comparing thoracic ducts seen in the second set of scans at the end of the year. Again the values on the chart are expressed as a percentage of the total number in the group (see Fig. 62).

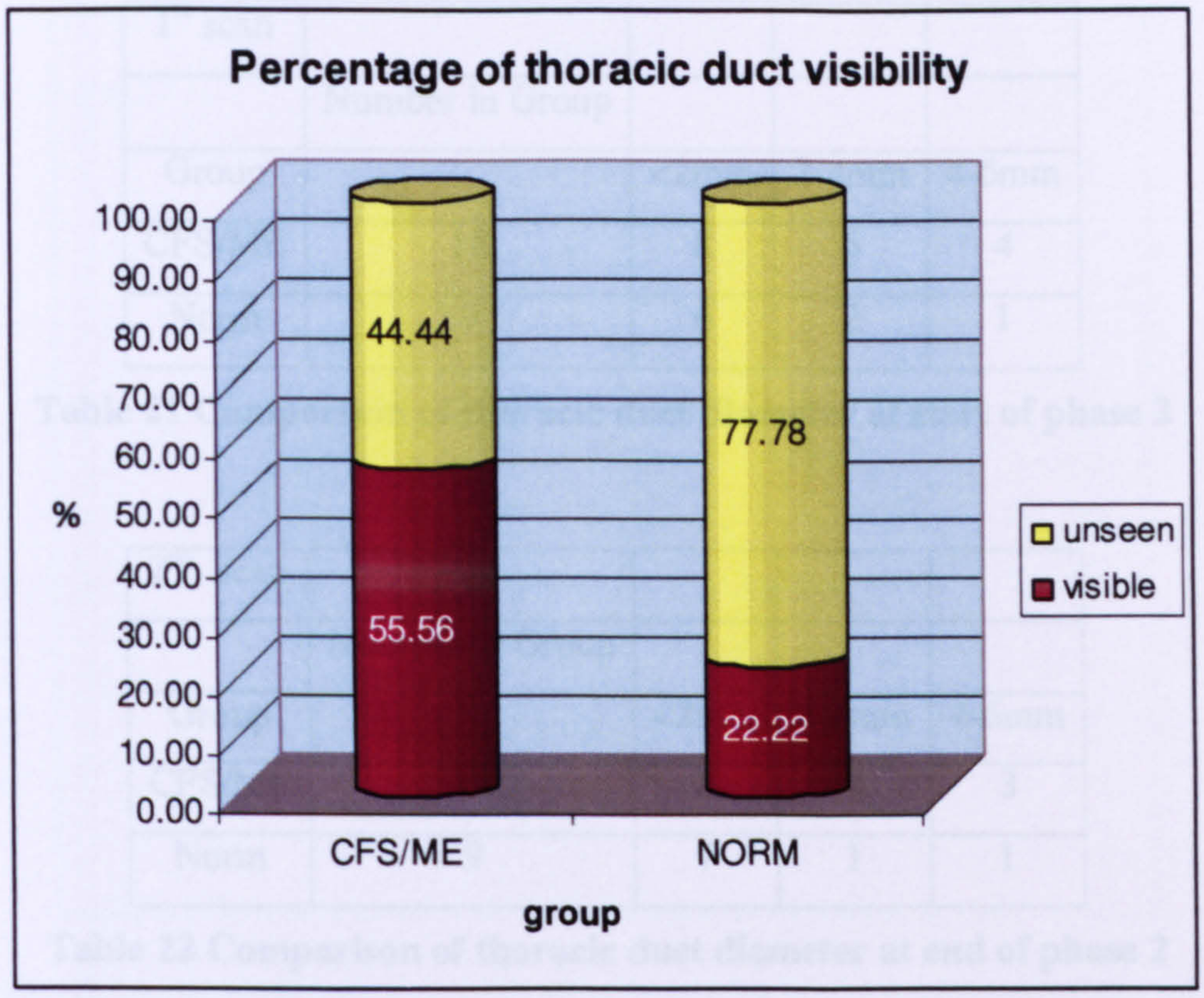



**Figure 62 Comparison of thoracic duct visibility at end of phase 2, expressed as a percentage**

The results were again statistically evaluated by a 2- sided Fisher's Exact test. The p-value at the end of the second phase = 0.2172, still insignificant.

The diameters of the thoracic duct lumen of the CFS/ME subjects and the healthy controls are compared in Tables 21 and 22, where < 2mm; 2-4mm and 4-6mm.

| 1st scan | | | | |
|---|---|---|---|---|
| | Number in Group | | | |
| Group | | <2mm | 2-4mm | 4-6mm |
| CFS/ME | 18 | 8 | 6 | 4 |
| Norm | 9 | 6 | 2 | 1 |

**Table 21 Comparison of thoracic duct diameter at start of phase 2**

| 2nd scan | | | | |
|---|---|---|---|---|
| | Number in Group | | | |
| Group | | <2mm | 2-4mm | 4-6mm |
| CFS/ME | 18 | 8 | 7 | 3 |
| Norm | 9 | 7 | 1 | 1 |

**Table 22 Comparison of thoracic duct diameter at end of phase 2**

Tables 21 and 22 differ due to:

1. RV05 in the patient group appearing narrower in the post-treatment scan at the end of the year.
2. The thoracic duct of NC07 from the healthy control group at the end of the year was not visible.

The pie charts below offer a clearer picture to the differences in the thoracic duct diameter between the groups with the Figs. 63 and 64 showing values at the start of phase 2 and the second set of pie charts Figs. 65 and 66 showing the sizes at the end of phase 2.

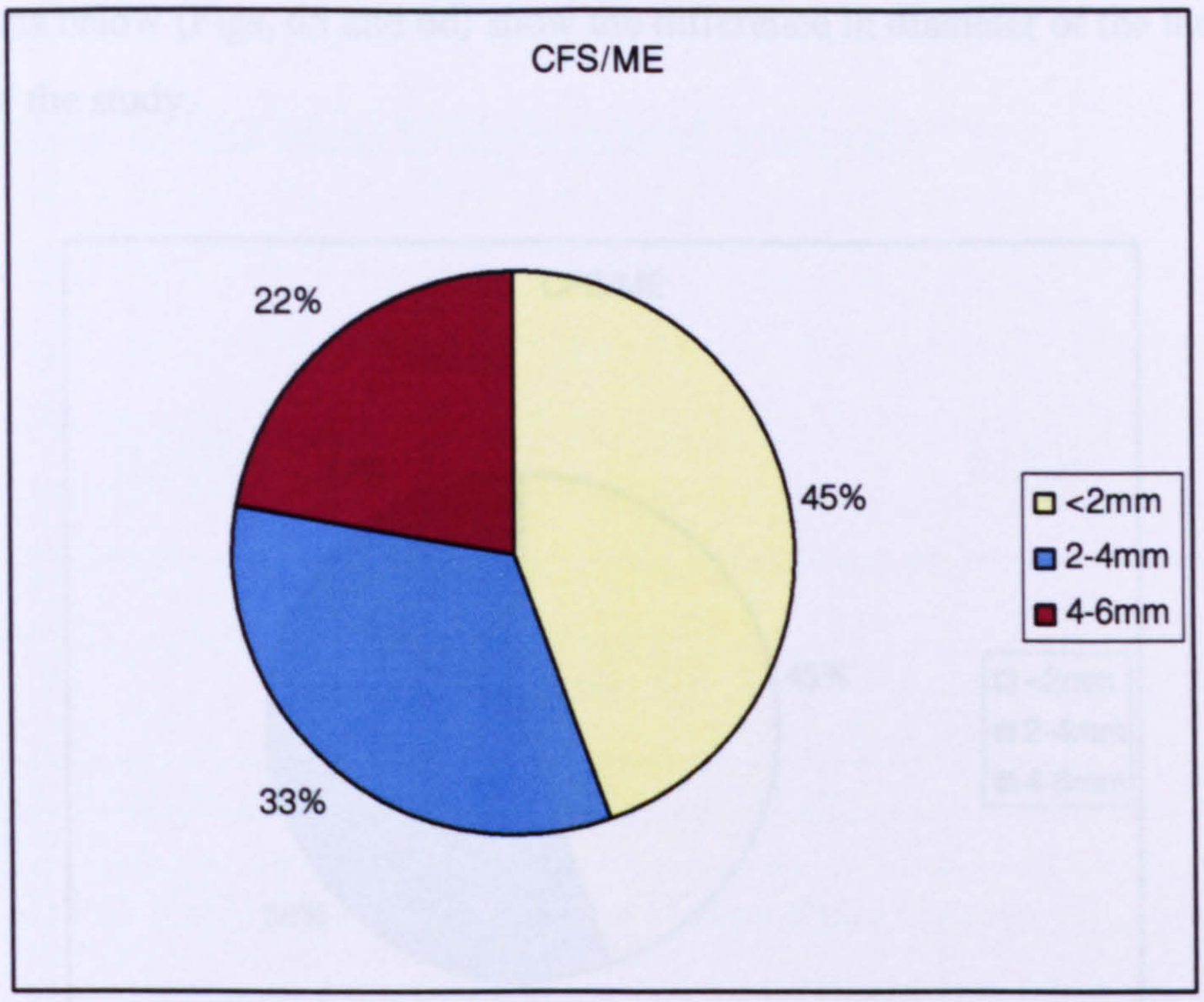



**Figure 63 Pie chart of thoracic duct diameter size in CFS/ME patients at start of phase 2**

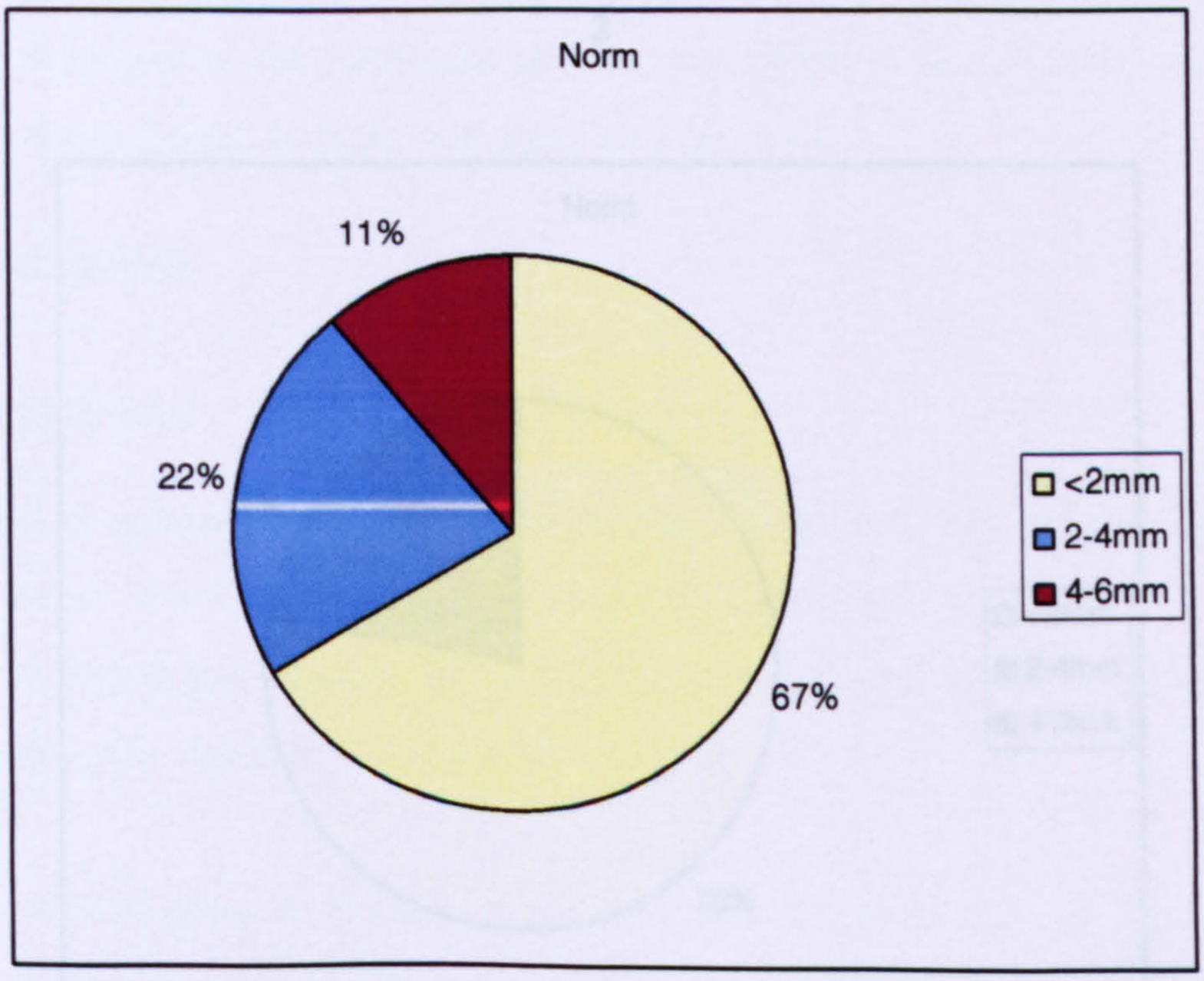



**Figure 64 Pie chart of thoracic duct diameter size in healthy control group at start of phase 2**

The pie charts below (Figs. 65 and 66) show the difference in diameter of the thoracic ducts at the end of the study.

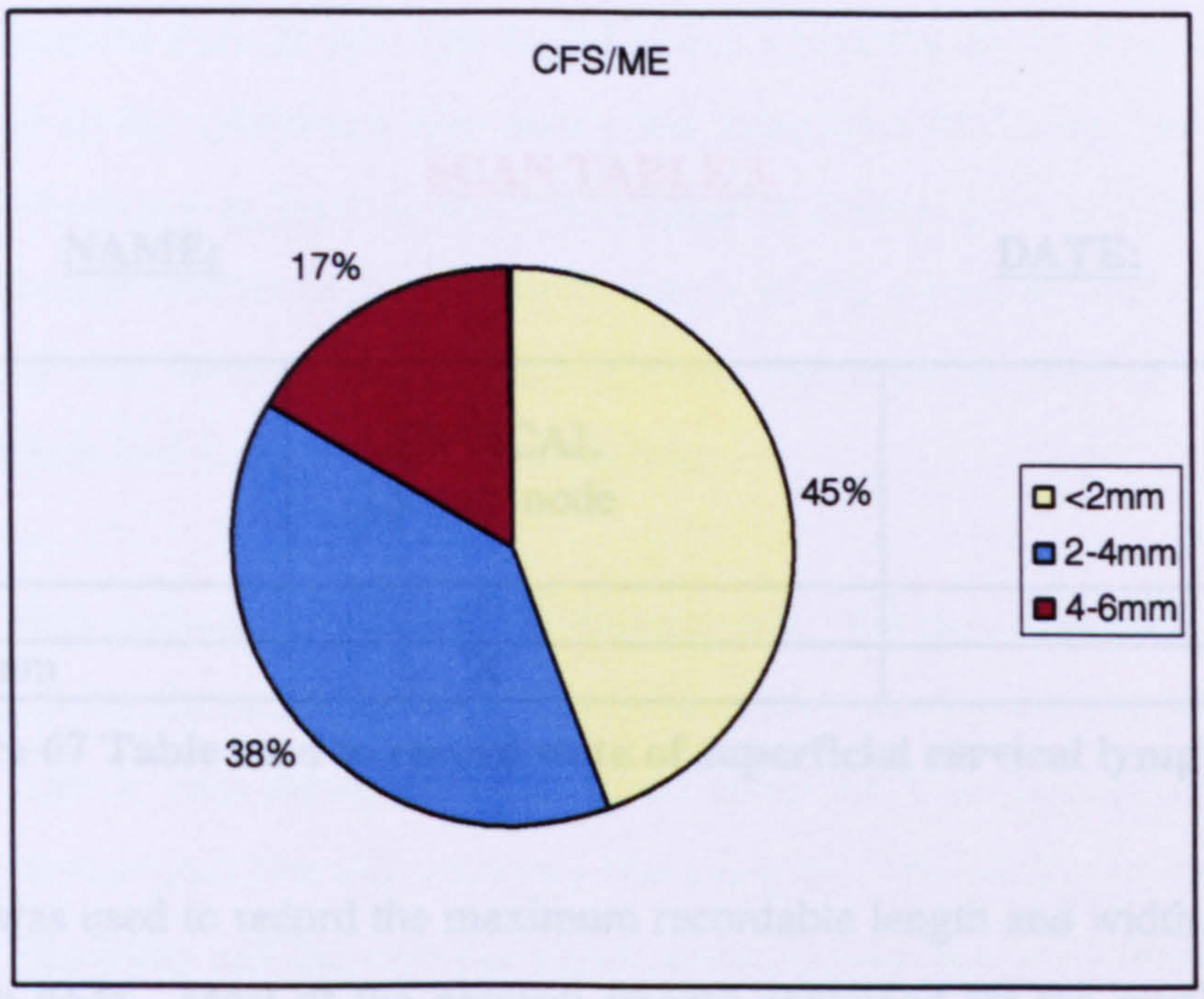



**Figure 65 Pie chart of thoracic duct diameter size in CFS/ME patients at end of phase 2**

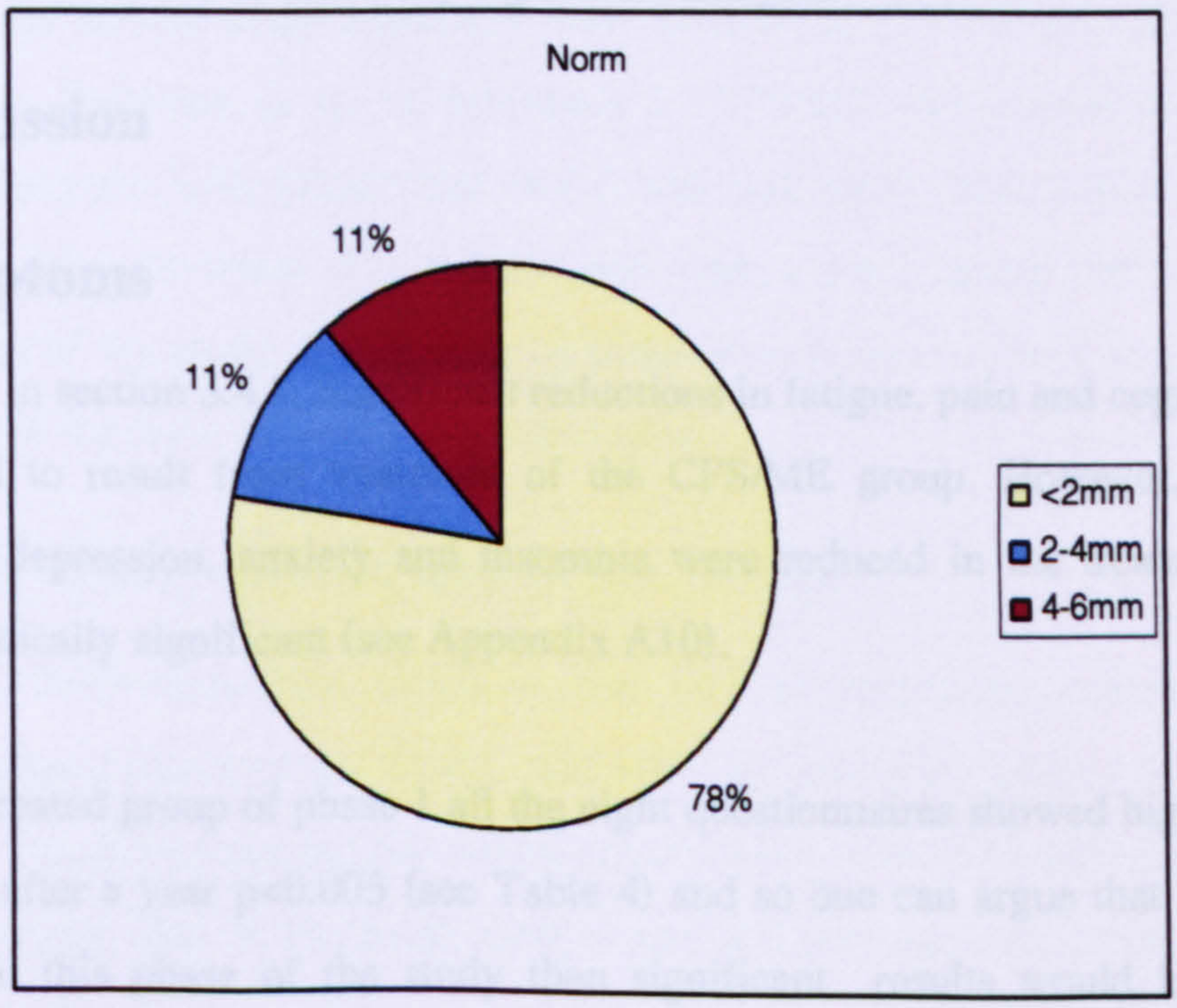



**Figure 66 Pie chart of thoracic duct diameter sizes in healthy group at end of phase 2**

## 3.4.4 Results of cervical lymph gland analysis

**SCAN TABLE 3.**

**NAME:** **DATE:**

| Code no:<br>Scan no:<br>Time: | CERVICAL<br>Lymph node | |
|---|---|---|
| Visual | | |
| Diameter/ mm | X | |

**Figure 67 Table used to record state of superficial cervical lymphatics**

Scan Table 3 was used to record the maximum recordable length and width of the scanned cervical lymph node. Most of the cervical images contained far too much flow artefact from neighbouring blood vessels to read clearly (see Fig. 51). Also, there was great difficulty in determining the difference between the lymph node and blood vessel, so not enough data was collected to make any significant analysis.

# 3.5 Discussion

## 3.5.1 Symptoms

As mentioned in section 3.4.1. Significant reductions in fatigue, pain and cognitive function were reported to result from treatment of the CFS/ME group. However, although the symptoms of depression, anxiety and insomnia were reduced in the treated group, they were not statistically significant (see Appendix A10).

In the larger treated group of phase 1 all the eight questionnaires showed highly significant improvement after a year $p<0.005$ (see Table 4) and so one can argue that if the numbers were larger in this phase of the study then significant results would have also been achieved in all the questionnaires.

It is interesting that the disorders examined in the four questionnaires that did not show significant improvement are mainly psychological symptoms related to depression and anxiety (see Appendix A6). If one was to claim that a placebo affect was the main reason for improvement in the symptoms then surely the symptoms of depression and anxiety in CFS/ME would improve as least as much as cognitive ability, pain and fatigue. The fact that there is a major difference in the improvement in the questionnaires gives credibility to the claim by the author that the osteopathic treatment is having some form of physiological affect and it is more than just placebo.

In addition to data collected by the physiological tests and questionnaires, patients were subjected to rigorous physical examinations by the author during treatment sessions which occurred up to once a week during the trial. It was noted that there was a palpable reduction in tone of the cervical and thoracic paravertebral muscles. The quality of movement in the thoracic spine improved and the cervical and thoracic lymphatics were less tender and less engorged following the year of treatment. Also the cranio-sacral rhythm had increased in amplitude and frequency in members of the treatment group.

The present part of the study examined four intracranial CNS abnormalities that have previously been indicated to be of relevance in CFS/ME and a number of additional parameters concerned with intracranial blood and CSF flow. Inter group differences in these abnormalities between two patient and one control group were examined at commencement of the study. The change in these abnormalities after 1 year duration was also subjected to the same inter-group comparisons.

## 3.5.2 Ventricular volume and brain atrophy

No significant differences were found in total CSF or ventricular volume between the groups at commencement of the study, and after the year-long study. All three groups showed a very small increase in CSF volume over 1 year, consistent with a small degree of age related atrophy. Due to the small sample size and non-parametric test employed, the statistical analysis may not be very sensitive to small changes in group CSF volume.

However the scatter plot of CSF proportion before and after 1 year gives no indication of differences between the 3 groups (Fig. 56). It is notable that 2 of the non-treated CFS/ME patients showed a marked change in CSF volume after 1 year, one significantly increasing and one significantly decreasing. Re-checking of the results and raw images confirms that these changes were genuine, however with only 2 time points one cannot be certain whether these changes were long term over the course of a year, or whether relate to shorter term fluctuations.

### 3.5.3 White matter abnormalities

As recorded in section 3.4.2.2, the groups showed low levels of WMH with no evidence of WMH in the basal ganglia or infratentorial structures in any patient with CFS/ME. Neither was there any significant change after a year even in the treated group.

The author's hypothesis maintains that the aetiology of CFS/ME is one of functional disturbance of the toxic drainage of the brain which is remedied by manual techniques to improve drainage but have no actual influence in the structure of the brain. Thus it has always been the view of the author that pathological brain lesions should not be found to occur any more in the CFS/ME patient than in the healthy person. This view contradicts previous research findings.

In a recent study using MRI, the images of 39 CFS/ME patients, 18 with psychiatric comorbidity and 21 without a psychiatric diagnosis since illness onset, were compared with 19 healthy controls (Lange *et al.*, 1999). The CFS/ME group with no psychiatric diagnosis showed a significantly larger number of brain abnormalities on T2 weighted images than the other two groups. The cerebral changes in the affected group consisted mostly of small, punctate, subcortical white matter hyperintensities, found predominantly in the frontal lobes. No significant difference was found when both CFS/ME groups were combined and compared to the HC group. The researchers, Lange *et al.*, (1999) suggested that any frontal lobe pathology could explain the more severe cognitive impairment previously reported in this subset of CFS/ME patients. The presence of WMH is a brain abnormality that has been seen in earlier research on patients with CFS/ME. As early as 1992 Buchwald and his

colleagues first reported subcortical hyperintensities in a group of CFS/ME patients (Buchwald *et al.*, 1992). These were observed again in 1995 by Cope and co-workers who noticed that the abnormalities were found more in a depressed control group than the CFS/ME group (Cope *et al.*, 1995). To complicate matters further, a year later Natelson and co-workers (Natelson *et al.*, 1993) following a similar study, reported that the abnormalities appeared more in the depressed group of CFS/ME patients.

Although an increase in WMH in CFS/ME patients was observed by Natelson (1993) and Buchwald (1992), in both studies some of the CFS/ME patients showed symptoms uncharacteristic of CFS/ME and suggestive of other disease factors. Lange *et al.*, (1999) found a significant increase in WMH in CFS/ME but only after splitting the CFS/ME group into those with and without DSM III-R Axis-I psychiatric disorder occurring since their CFS/ME diagnosis, the increase being found in the group with no Axis-I psychiatric disorder. On the other hand some studies have failed to find any significant difference in the presence of WMH in CFS/ME patients and controls (Cope and David, 1996; Schwartz *et al.*, 1994).

In the present study all subjects in patient and control groups were subjected to a thorough screening to ensure the absence of any psychiatric disorder including detailed consultation with a psychiatrist. Scoring of DWMH with a widely used semi quantitative scale demonstrated only small numbers of white matter abnormalities with no difference between experimental groups and no evidence of change over time.

The clinical relevance of these white matter hyperintensities remains unclear but we now know that they may occur in clinically normal individuals due to increasing age or when the person is diabetic, suffering from hypertension or cardiac disease (Schmidt *et al.*, 1996). It is the belief of the author that the conclusions of the previous studies which assumed the abnormalities to be due to the CFS/ME did not take into account a multitude of other factors which could have led to the formation of these hyperintensities.

It would be prudent to conclude that success of osteopathic treatment advocated by the author for the treatment of CFS/ME is not due to the eradication of damaged brain cells. There is no evidence to imply such an implausible effect of manual therapy. What is suggested is that by stimulating fluid drainage of the brain the probable outcome is a reduced level of toxicity which aids normal cerebral function. This viewpoint is supported by the results of this study which demonstrate that pathological brain lesions do not occur any more in the CFS/ME patients compared with the healthy normal control group.

## 3.5.4 Blood and CSF flow

During the cardiac cycle, the transient increase in blood volume in the skull is balanced by an outflow of CSF through the cerebral aqueduct. The mechanical coupling between arterial and CSF flow pulsations has a dampening effect dependant on the compliance of the blood vessels and surrounding tissues. Cerebrovascular disease may lead to alterations in this vascular compliance with corresponding alterations in the pattern of CSF pulsatility in the aqueduct. This can be considered a sensitive but non-specific indicator of small vessel disease in the brain.

In this study the temporal dynamics of blood flow into the brain and the corresponding CSF flow pulsations through the cerebral aqueduct demonstrated no significant differences for any of the flow associated parameters tested. Thus no evidence was detected of small vessel disease in the brain associated with CFS/ME.

## 3.5.5 Thoracic duct visibility

Tables 19 and 20 and their associated charts (Figs. 61 and 62) show an increase in the visibility of the thoracic duct when comparing the CFS/ME scans with the healthy group at the start and end of the year. However, statistically this improvement has not been shown to be significant. This may very well be due to the small number of subjects which makes statistical significance difficult. Nevertheless, there is a definite trend showing an enlarged lumen diameter of the thoracic duct of in CFS/ME patients supporting the hypothesis that in CFS/ME retrograde flow may lead to lymphatic congestion in the thoracic duct. This trend is further supported when examining the diameter size of thoracic ducts which are

seen to be generally wider than those seen in the healthy group (tables 21 and 22), also shown in the pie charts (Figs. 63 and 66).

# Chapter 4

# 4 Assessment of the osteopathic method for the treatment of CFS/ME: Phase 3; further analysis of muscle fatigue

## 4.1 Introduction

In phase 1 of this study (see chapter 2) the initial assessment of muscle fatigue showed that the treatment did improve this major symptom. The aetiological process and pathophysiological mechanisms that lead to generalised abnormal muscle fatigue after relatively mild activity were undetermined by the first phase. Consequently in phase 3, which ran concurrently with phase 2, the possible myophysiological processes that could account for the fatigue in CFS/ME were investigated.

Paul et al. (1999) investigated the delayed recovery from fatiguing exercise in CFS/ME patients. Recovery was assessed following three sessions of ten maximum voluntary isometric contractions over a 24 hour period. In this study, Paul and co-workers found that the healthy control group showed no significant difference in all three test sessions whereas the patient group showed a significant increase in recovery time as they progressed through the 24 hour period.

Functional electrical stimulation (FES) of the quadriceps might have provided a more accurate way of measuring fatigue as it could produce a set level of stimulation in the muscle (Bajd et al., 1990). However, it was felt that FES would have been too painful for these patients to withstand, and for ethical reasons we preferred to use active contraction controlled by the patient.

Abnormal single fibre electromyography has been seen in about 75% of 40 patients with CFS/ME indicating abnormality in the motor unit (Jamal and Hansen, 1985). The muscle fibre was considered the likely site of involvement although there was no abnormality of fibre density noted. Jamal and Hansen (1985) suggested that a defect in the muscle

membrane following a persistent viral infection via myogenic enzymic activity was a possible cause of the fatigue. Earlier findings in muscle biopsies taken from 20 CFS/ME patients suggested widespread minor necrotic and microscopic structural changes (Behan et al., 1985). On the basis of these findings, it was concluded that EMG studies were essential in the present study to exclude any other neurogenic or myopathic aetiologies of fatigue

This stage of the study, as in phase 1, mainly focused on the maximum torque produced and whether this could be sustained over a set period of time. This was determined by calculating the area under the torque versus time graph (impulse torque). Impulse torque was inversely proportional to the fatigue of the muscle and so was a suitable method for determining the fatigability of the knee extensors. The maximum force applied by the muscle was also examined. It was important to avoid any muscle damage or unnecessary pain for the subject. Subsequently, as in phase 1, after thirty seconds of the final push, the patient was told to stop. However, in the actual test some subjects accidentally stopped fractionally before the thirty second mark and so the impulse torque was calculated over the initial twenty seconds.

As in the earlier phase of the study, the subjects' final push was rated according to the Borg Scale of Perceived Exertion (see Appendix A7) (Borg and Linderholm, 1970). Furthermore the difference between real and perceived exertion during the initial tests were compared with the final test to guard against the possibility that subjects may exert more effort at the end compared to the beginning of the trial.

## 4.2 Aims of phase 3

This part of the study aimed to further evaluate the efficacy of the novel manual treatment protocol for CFS sufferers. Changes in exercise induced fatigue pre and post treatment were assessed. The objectives were to quantify and identify the source of muscular fatigue from the peak torque, impulse torque and sEMG signal measured during the isometric contraction of quadriceps thereby determining if there is any pathology in the muscles that may be causing the symptom of fatigue in CFS/ME, and to determine whether any of the major CFS/ME symptoms were improved following the manual treatment protocol.

## 4.3 Methods

### 4.3.1 Isometric dynamometry

Knee extensor tests were carried out using a Kin-Com AP isokinetic dynamometer (see Figs. 68 and 69). This equipment has been validated in many prior research studies (Poulin, 1992; Bennett and Stauber 1986 and Weltman *et al.*, 1986). The system's reliability and validity was found to be 0.94 to 0.99 for both static and dynamic exercises (Farrell and Richards, 1986).

On these grounds a plethora of publications exist on the use of such devices to investigate quadriceps function. Isometric torque produced by the quadriceps has been shown to be a useful measure of recovery in muscle function pre and post treatment. Peak torque during voluntary quadriceps muscle strength tests have been measured following knee injury (Holder-Powell *et al.*, 1999); and during recovery of muscle strength after high tibial osteotomy (Kawazoe and Takahashi, 2003). Agre *et al.*, (1997) investigated the efficacy of a 12-week home quadriceps muscle strengthening exercise program by investigating isometric torque and endurance. To assess endurance these authors used a measure of tension time index (TTI) defined as being the product of isometric endurance time and 40% of maximal torque.

Subjects were seated comfortably in the dynamometer chair with the tibia at 90 degrees to the thigh, and an angle of 90 between the alignment of the spine and the femur. The pelvis was stabilised with a seatbelt and the right thigh with a wide Velcro strap. The centre of rotation of the knee was aligned with the axis of rotation of the dynamometer lever (see Figs. 68 and 69).

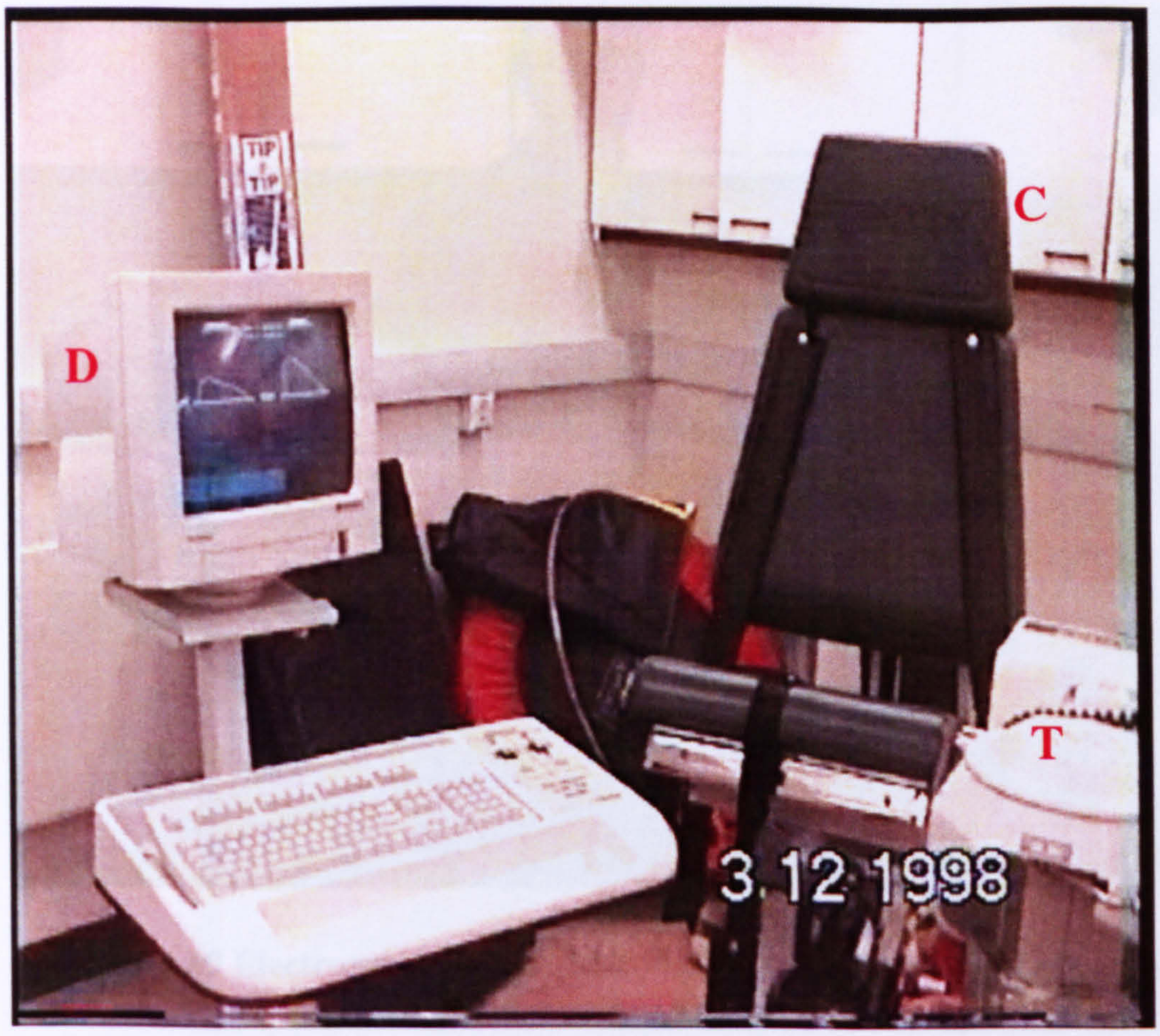



**Figure 68 The Kin-Com dynamometer at Salford University's human kinetics laboratory**

**C** = Chair in which patient is strapped loosely in to stop unnecessary movement.

**D** = Display unit (showing Force V time graph and giving visual instruction to operator).

**T** = Torque Transducer connected to the pressure pad (via lever arm) and the computer.

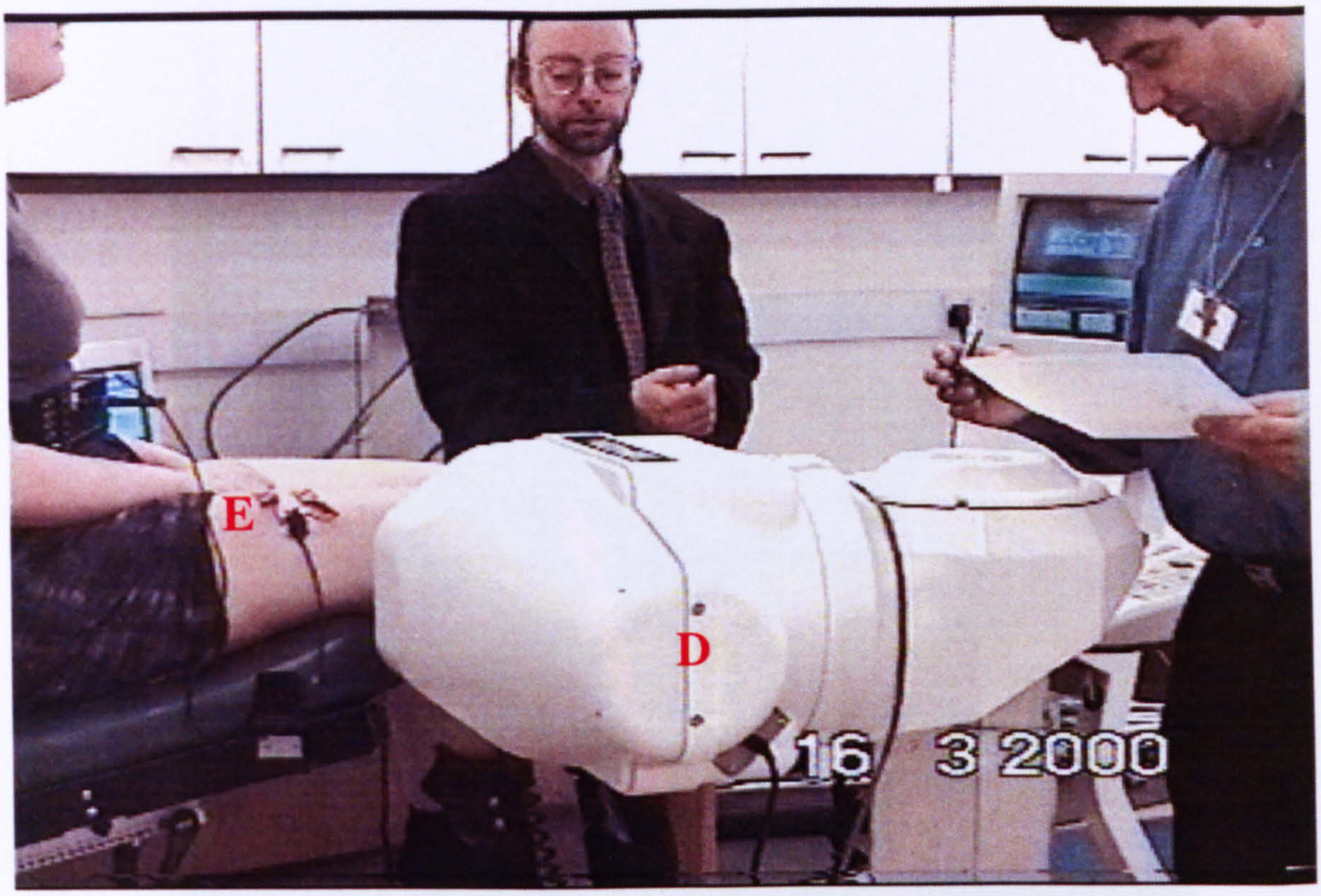



**Figure 69 Electromyography and isometric dynamometry of the subject's right quadriceps**

E = Electrodes of surface EMG strapped to subject's right thigh.
D = Dynamometer (transducer, converting torque into electrical signal)

The lever attached to a torque transducer at the level of the knee joint axis was aligned along the lateral side of the leg with a padded lever arm extending in front of the shin, just above the ankle. Torque data was collected at a sample rate of 100 Hz. During each measurement the patient was seated with the leg hanging vertically with the lever. The seat, placed in the same fixed position for all tests on that particular subject who was asked to exert as much force as possible against the lever arm (see Fig. 70). The resulting trace of torque at the knee was plotted against time by the system's computer. After a set period of time the subject was instructed to stop pushing.

Calibration of the pressure pad position along the longitudinal axis of the lever arm took place before each test to maintain constant distance from the torque transducer (see Fig 70). Note that when the subject was seated the lever arm was placed in the vertical position parallel with the lower leg.

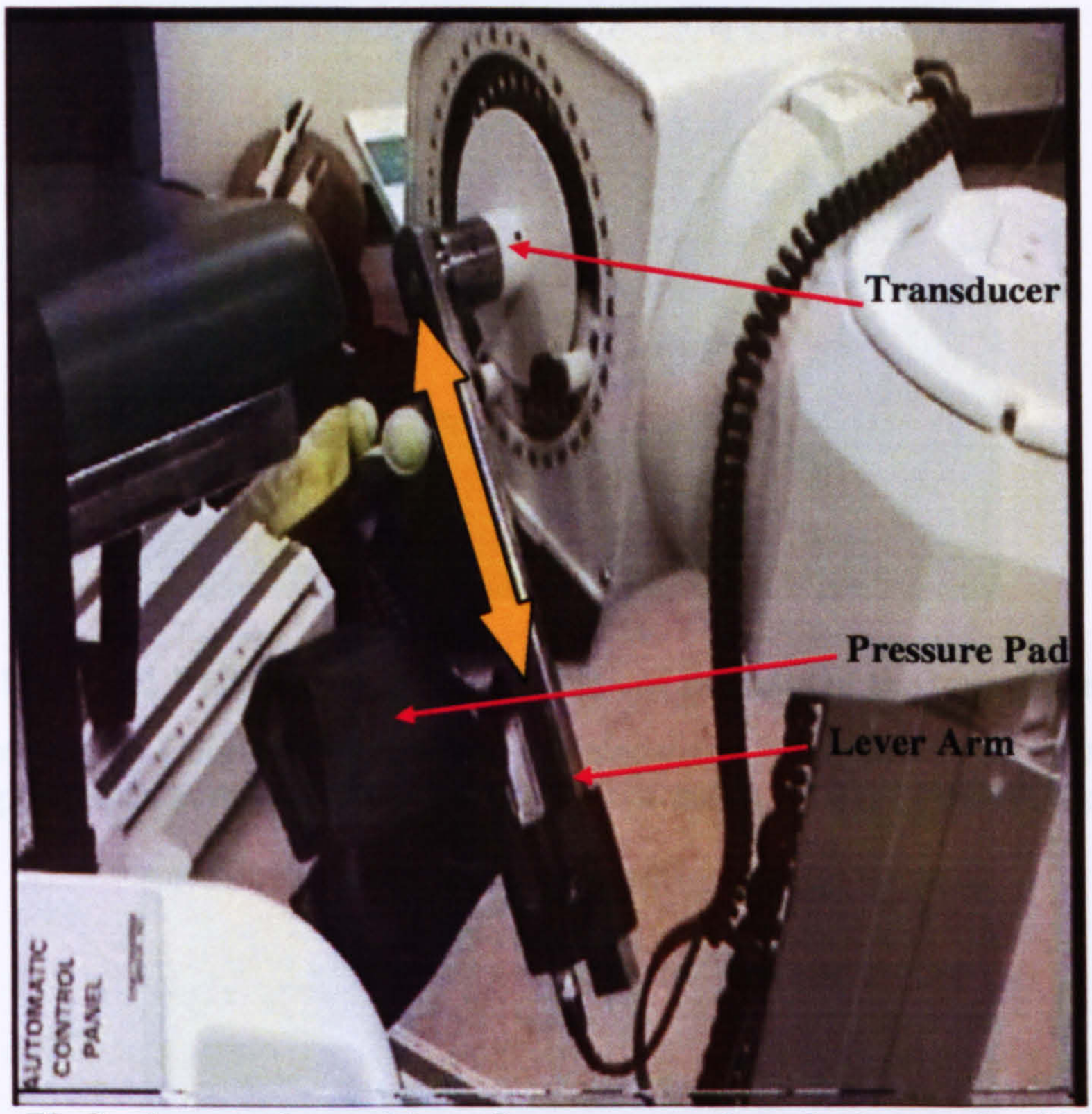



**Figure 70 Setting up the position of pressure pad on the long axis of lever arm**

The pressure pad was manually adjusted to attach to the same point on the subjects lower leg both at the start of the study and 12 months later.

Before each test the angular position of the base of the transducer was also rotated to a preset positioned (Fig. 71). The base was also moved in both A/P and lateral planes to keep the position of the dynamometer a constant in both tests (Fig. 72).

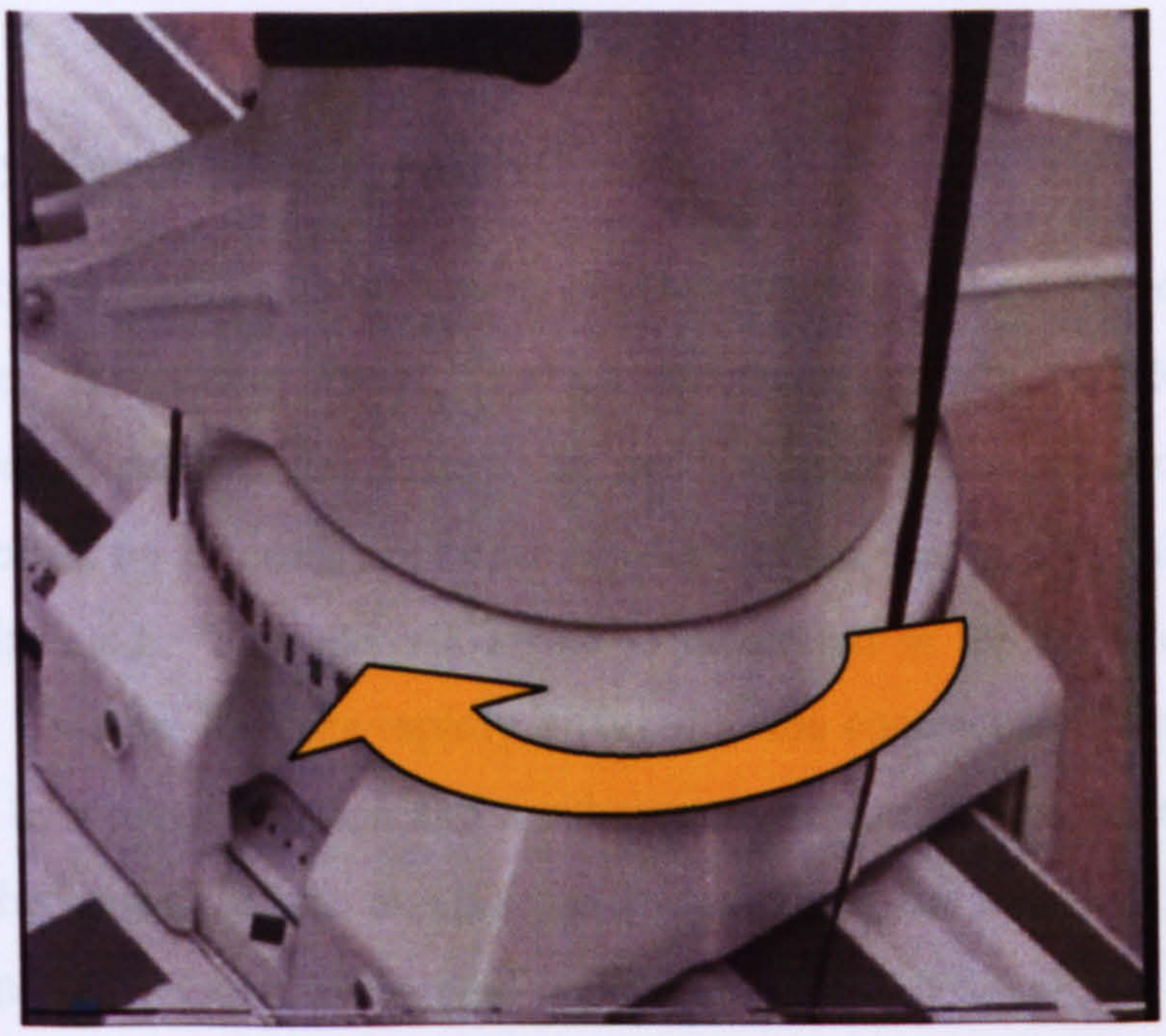


**Figure 71 Fixing the angular position of the base of the transducer**

The base of the Kin-Com's transducer was adjusted using the machine's automatic control panel and positioned at the same angle at the start of the study and 12 months later.

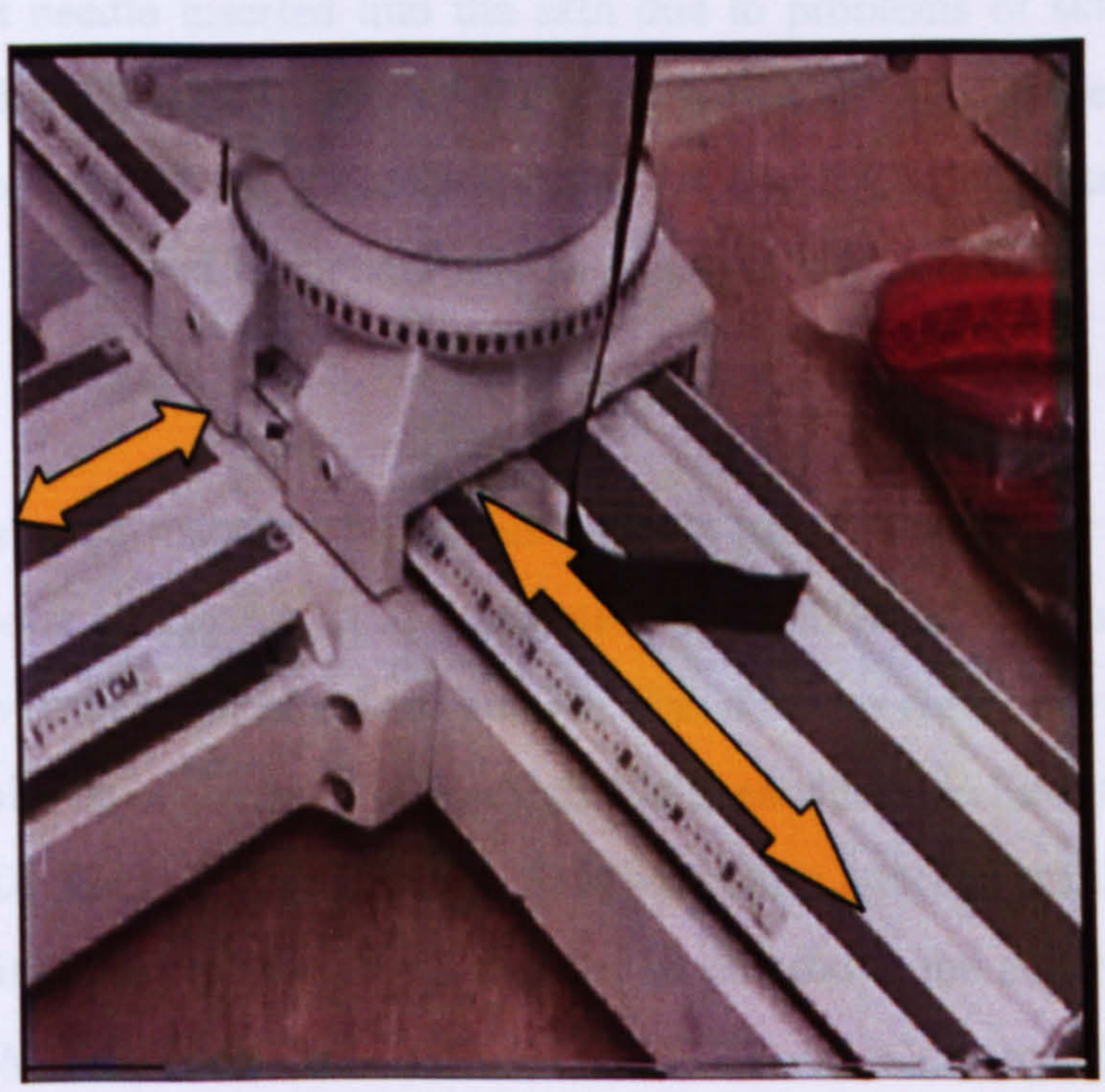


**Figure 72 Fixing the a/p and lateral position of the base of the transducer**

The base of the Kin-Com's transducer was adjusted using the machine's automatic control panel and moved to the same position at the start of the study and 12 months later.

## 4.3.2 Surface electromyography

"Electromyography provides easy access to physiological processes that cause the muscle to generate force" (De Luca, 1997). Surface electromyography (sEMG) was used to monitor the action of the muscles tested. In every muscle there are a number of motor units, each controlled by a motor nerve which depolarises the muscle initiating a muscle action potential (m.a.p.). This electric signal is generated in the muscle fibre when the muscle contracts. Calcium ions are rapidly diffused to the contractile filaments of actin and myosin resulting in a depolarisation and a subsequent repolarisation wave along the fibre. EMG measures the sum of all the m.a.p.s transmitted along the muscle fibres at that point in time. The frequency of an EMG signal is the rate at which the signal oscillates up and down, produced from twitching of muscle fibres (Winter, 1979).

Surface electromyography utilises electrodes stuck to the skin surface. This is not as accurate as using a needle inserted into the skin due to problems of skin resistance and cross talk from other muscles. However the surface method was chosen purely due to ethical considerations (i.e. it was painless and non-invasive). The quantitative relationship between the EMG signal and force can only be assessed with isometric contractions (De Luca, 1997).

The sEMG signals were recorded for rectus femoris using silver/silver chloride surface electrodes in a bipolar configuration at a sample rate of 1000 Hz, with an inter-electrode distance of 2 cm over the belly of rectus femoris. The skin was cleaned with electrode skin preparation. The midline of the belly of a muscle has been shown to have the greatest EMG signal amplitude (De Luca, 1997). Thus the electrodes were attached parallel to the muscle fibres on the longitudinal midline of the muscle 10 cm above the superior border of the patella. Surface EMG data was collected with an MT8 radio telemetry EMG system (MIE Medical Research Ltd.). The signals from the electrodes were processed through differential amplifiers (gain of 4,000, Common Mode Rejection Ratio= 110 dB, and bandwidth of 4-1000 Hz).

In any EMG signal there is a range of frequencies of the muscle fibre twitches. These frequencies can be calculated from a graph of time plotted against the magnitude, also referred to as the amplitude, measured in microvolts (Fig. 73). However this is not directionally proportional to the force in the muscle.

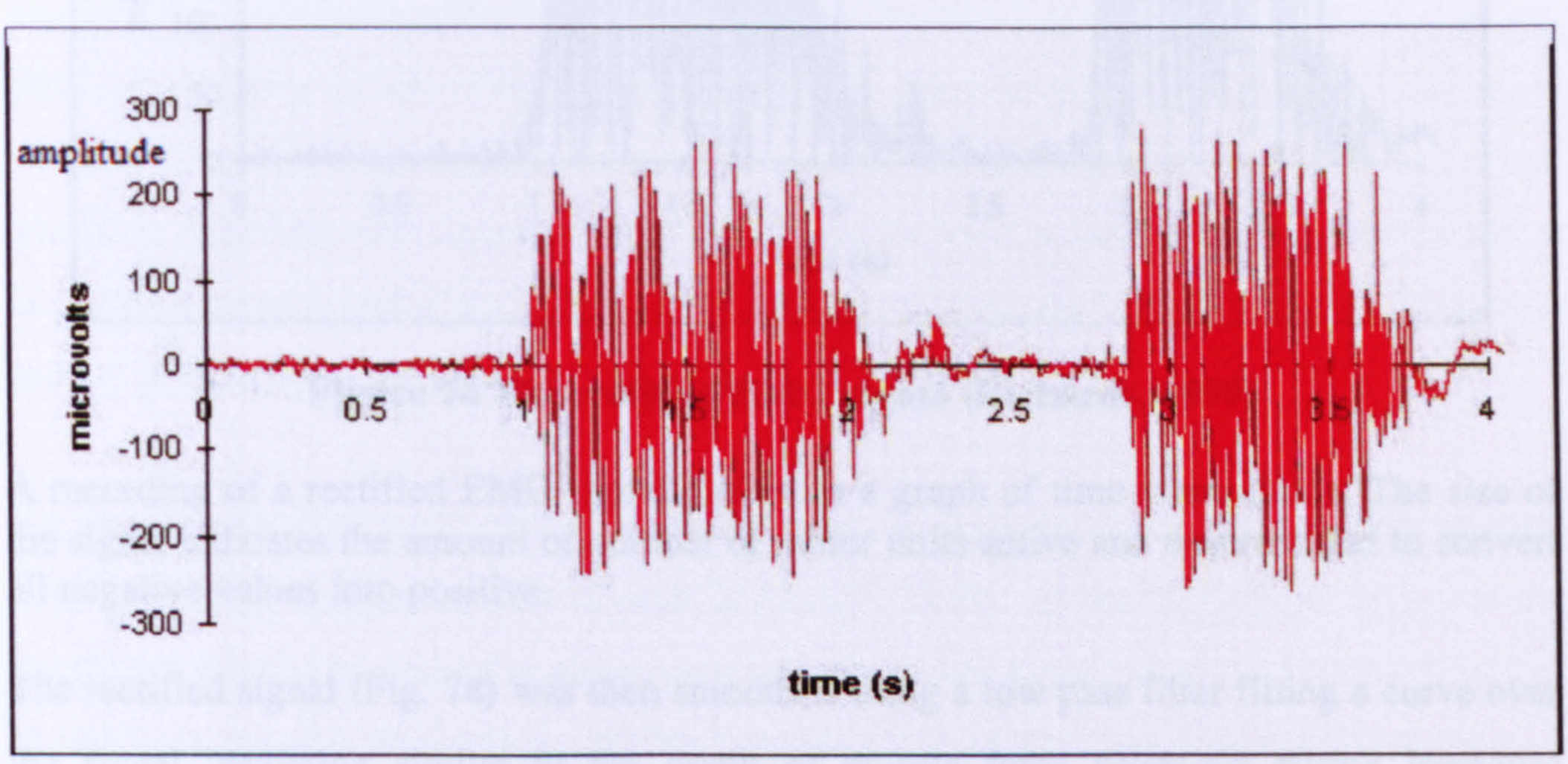



**Figure 73 The raw EMG signal (Richards, 1999)**

A recording of a raw EMG signal plotted in a graph of time v amplitude. The interference from mains electricity is reduced by amplifying the signal close to the electrodes and by filtering. The size of the signal indicates the amount of number of motor units active.

The graph above was rectified to convert all negative values into positive to give the recording shown in figure 74. The graph is again of time in seconds plotted against the amplitude, measured in microvolts.

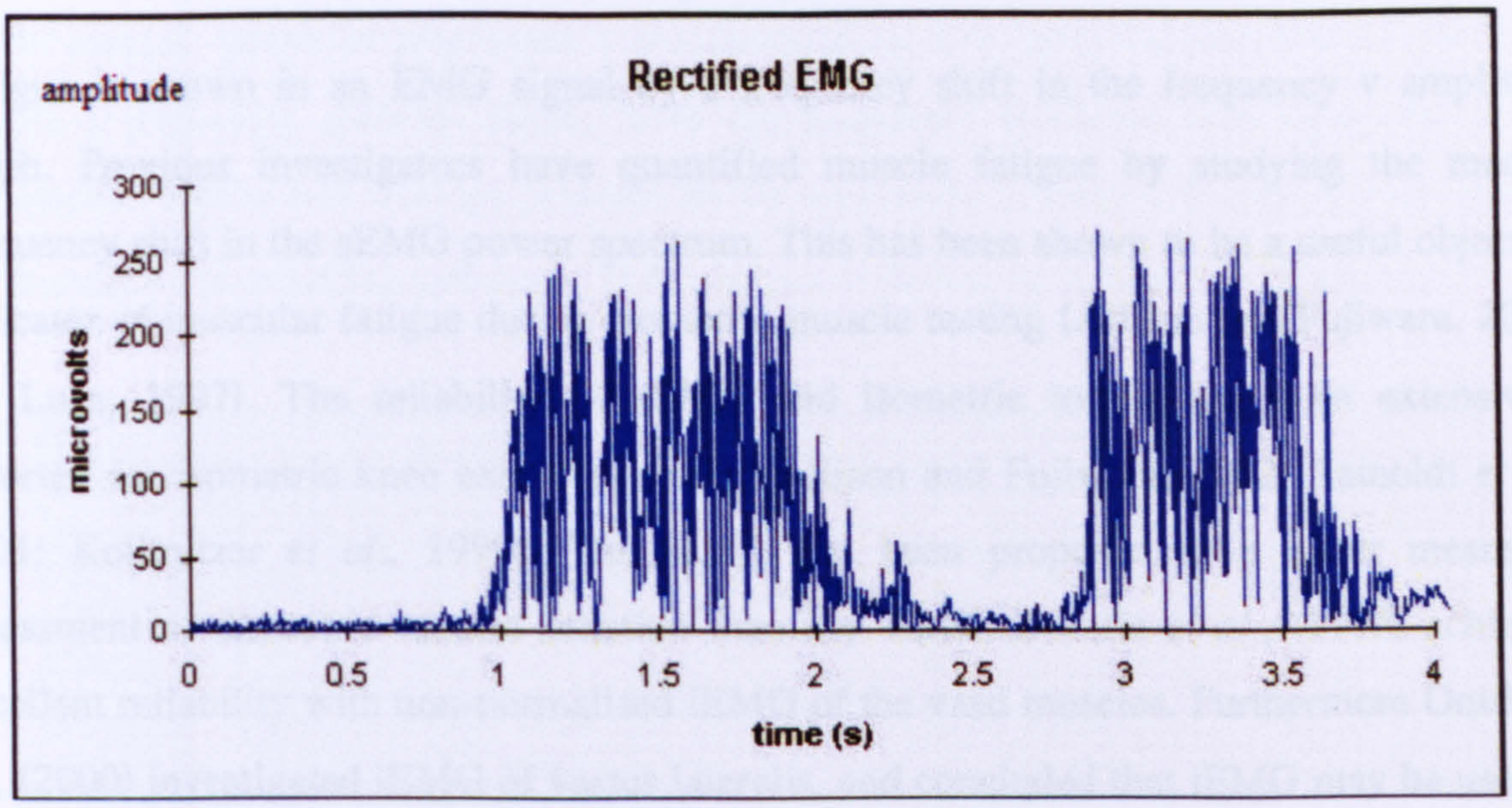



**Figure 74 The rectified EMG signal (Richards, 1999)**

A recording of a rectified EMG signal plotted in a graph of time v amplitude. The size of the signal indicates the amount of number of motor units active and was rectified to convert all negative values into positive.

The rectified signal (Fig. 74) was then smoothed using a low pass filter fitting a curve over the signal becoming similar to the graph of muscle force produced during isometric contractions by the Kin-Com. The area under this rectified enveloped graph (Fig. 75) gives the value of the integrated EMG (iEMG).

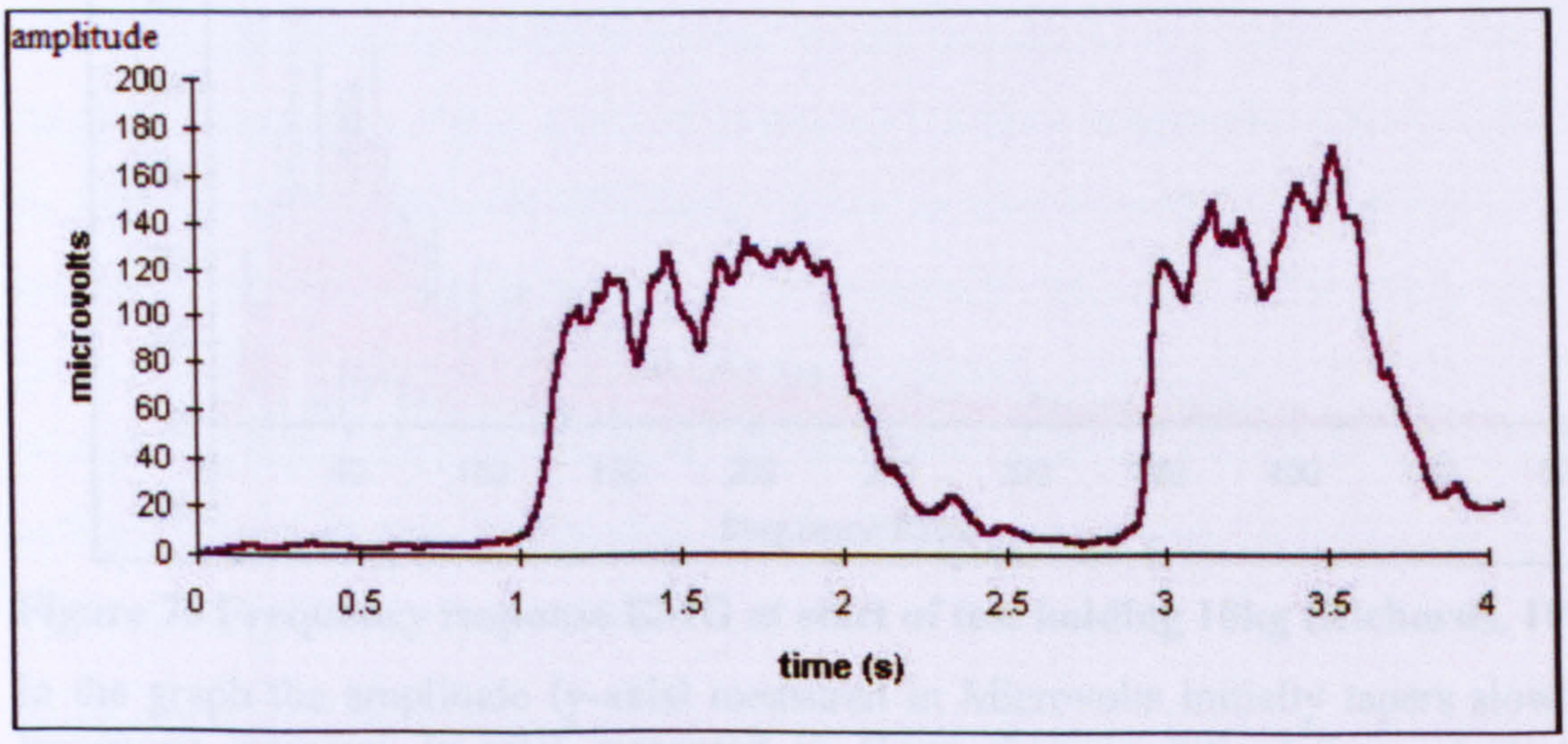



**Figure 75 Enveloped EMG signal (Richards, 1999)**

A rectified enveloped graph of time v amplitude, formed by using a low pass filter over the rectified EMG signal. The area under the graph is known as the integrated EMG.

Fatigue is shown in an EMG signal by a frequency shift in the frequency v amplitude graph. Previous investigators have quantified muscle fatigue by studying the median frequency shift in the sEMG power spectrum. This has been shown to be a useful objective indicator of muscular fatigue during isometric muscle testing (Allison and Fujiwara, 2002; De Luca, 1997). The reliability of sEMG and isometric torque has been extensively reported for isometric knee extensor testing (Allison and Fujiwara, 2002; Rainoldi *et al.*, 2001; Kollmitzer *et al.*, 1999). The iEMG has been proposed as a better means of assessment of isometric muscle function than raw EMG. Zakaria *et al.*, (1996) achieved excellent reliability with non-normalised iEMG of the vasti muscles. Furthermore Onishi *et al.*, (2000) investigated iEMG of vastus lateralis, and concluded that iEMG may be used to predict muscle force in kinesiological research.

An example of frequency shift is seen below in an isometric test on a healthy subject holding a 10kg weight for one minute (Richards, 1999). In the first graph (Fig. 76) the amplitude (y-axis) measured in Microvolts initially tapers slowly as the frequency increases (x-axis) measured in Hertz showing little fatigue at start of this isometric test.

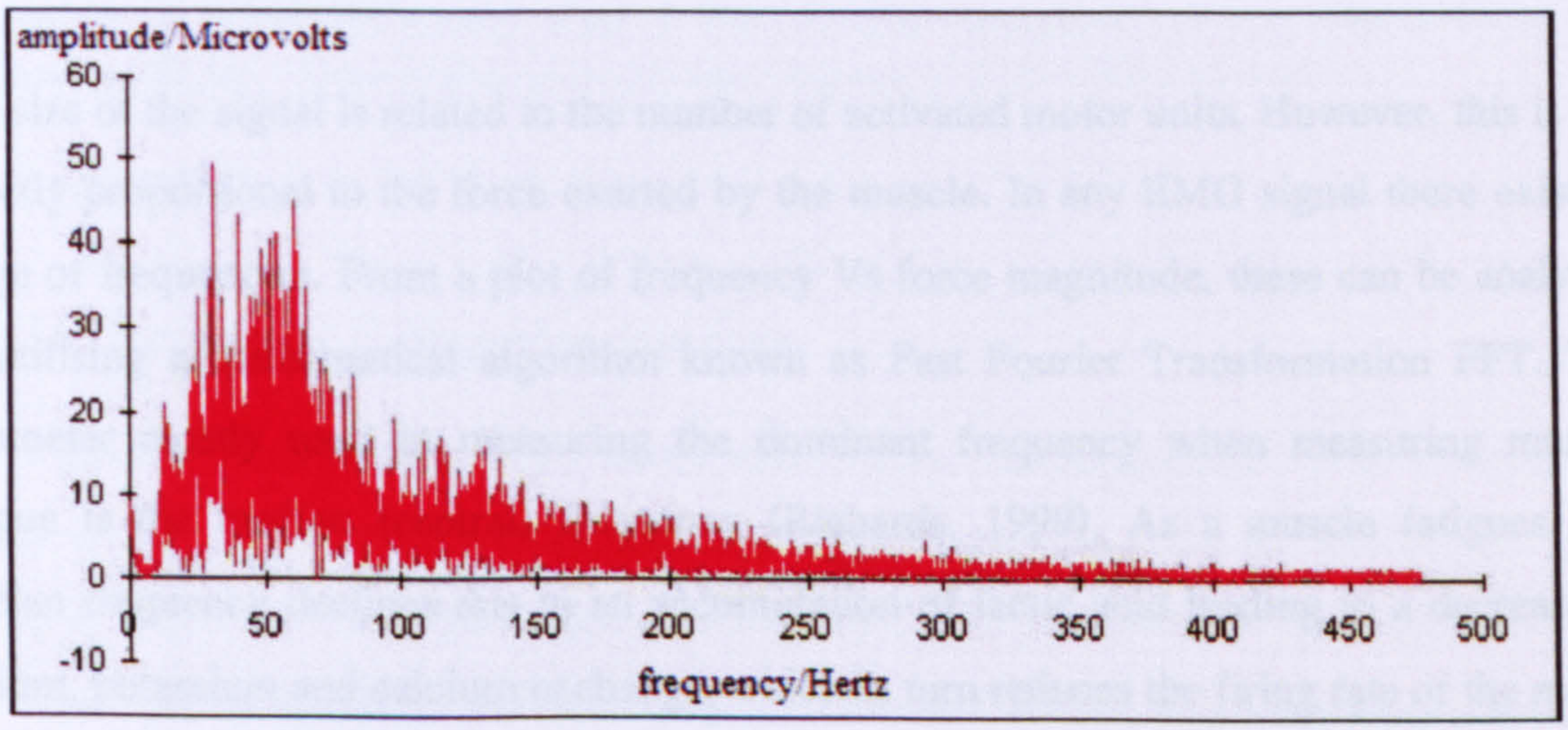



**Figure 76 Frequency response EMG at start of test holding 10kg (Richards, 1999)**

In the graph the amplitude (y-axis) measured in Microvolts initially tapers slowly as the frequency increases (x-axis) measured in Hertz showing little fatigue at start of this isometric test.

In the second graph of amplitude v frequency (Fig. 77), after holding the weight for 1 minute a frequency shift is shown, with the frequency spectrum moving to the lower frequencies on the left with an increase in the amplitude (y-axis/ μV) tapering quickly as the frequency (x-axis/Hz) increases. This frequency shift is an indication of fatigue.

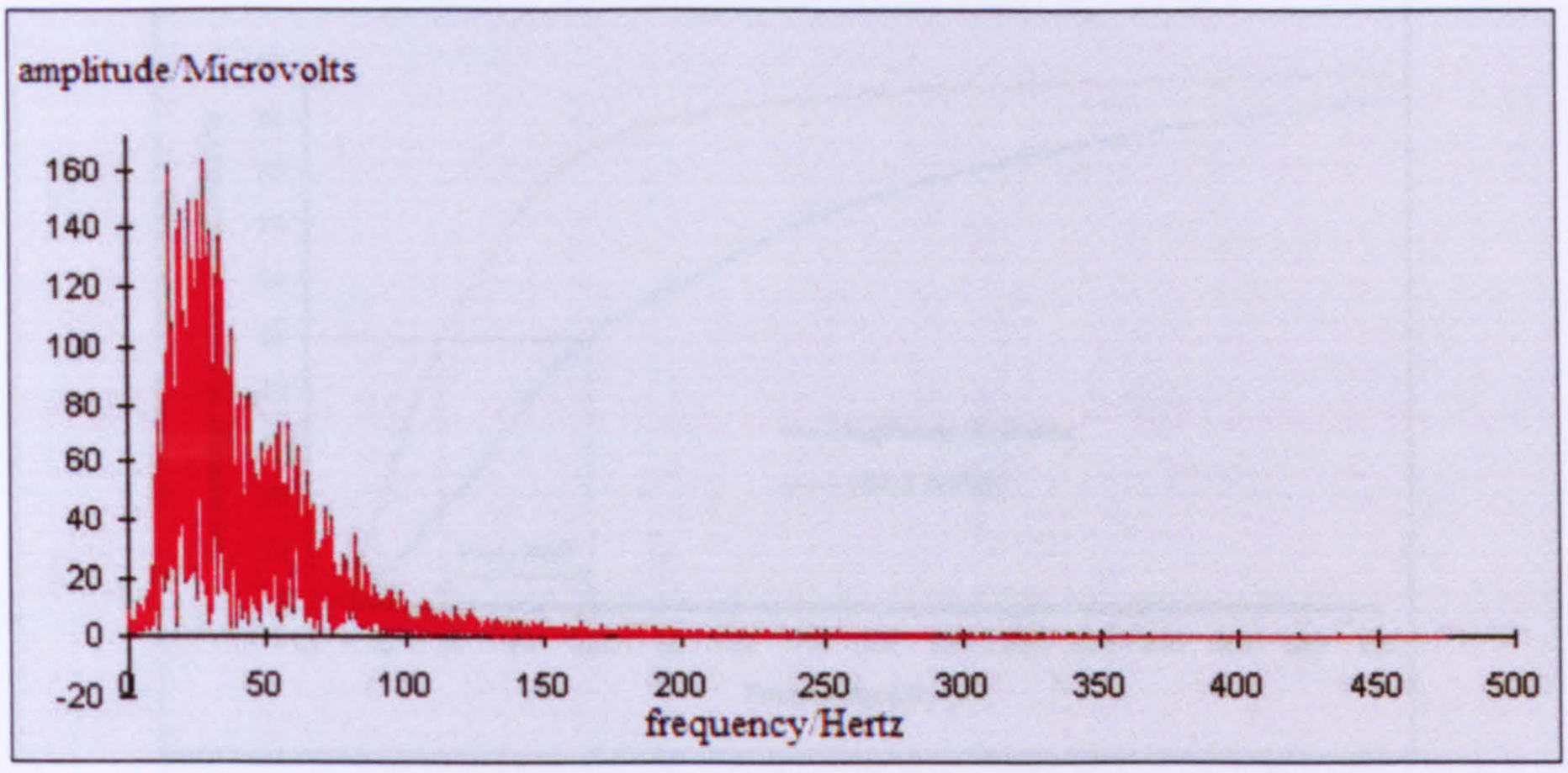



**Figure 77 Frequency response EMG while holding 10kg after 1 min (Richards, 1999)**

In the graph of amplitude v frequency, after holding the weight for 1 minute fatigue has been shown indicated by a frequency shift to the left with an increase in the amplitude (y-axis/ μV) tapering quickly as the frequency (x-axis/Hz) increases.

The size of the signal is related to the number of activated motor units. However, this is not directly proportional to the force exerted by the muscle. In any EMG signal there exists a range of frequencies. From a plot of frequency Vs force magnitude, these can be analysed by utilising a mathematical algorithm known as Fast Fourier Transformation FFT. The parameter mostly used in measuring the dominant frequency when measuring muscle fatigue is the median (central) frequency (Richards, 1999). As a muscle fatigues, the median frequency declines due to an accumulation of lactic acid leading to a decrease in sodium, potassium and calcium exchange, which in turn reduces the firing rate of the motor units (Allen, 2004; Renaud, 2002).

Frequency was plotted against the amplitude of the signal, which in this context is referred to as the 'power' of the signal. The power spectrum is a plot of the portion of a signal's power falling within given frequencies. The median frequency is then calculated as the

frequency when the power is at 50% of maximum. The difference between the frequency value at 50% of power before and after exercise/activity is the frequency shift and is an accurate indicator of muscle fatigue as demonstrated in the example shown in figure 78.

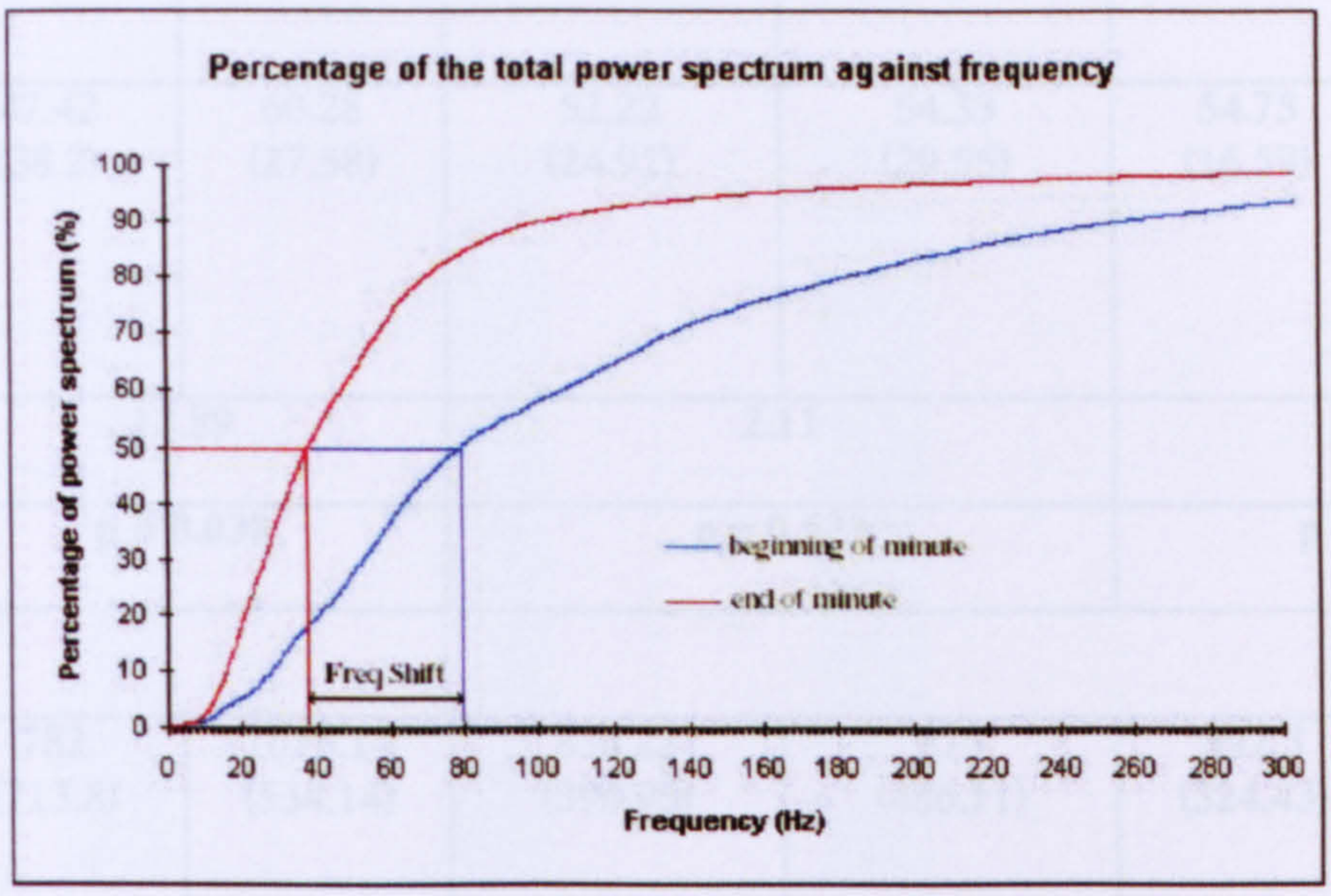



**Figure 78 Calculating the frequency shift (Richards, 1999)**

In the graph of power spectral density v frequency, after holding a weight for 1 minute fatigue is shown by the frequency shift indicated by 50% of the maximum signal being reached at a lower frequency after 1 min (40Hz) compared to the frequency at the beginning (80Hz). Thus in this example the frequency shift = 80 – 40 = 40Hz.

## 4.4 Results

### 4.4.1 Torque and impulse torque

In the present study, which was a single-blind study, measurement of peak and impulse torque in the treated patient group increased significantly over the 12 month period, as shown in Table 23. The peak torque increased by 27% (p=0.038), and the impulse torque increased by 29% (p=0.027; column 1 and 2). This indicates an improvement in the ability of quadriceps to produce torque and sustain it during the maximal push following treatment. No significant changes were seen in either the untreated patient group or the normal control group (Columns 3, 4 and 5 and 6).

| | TREATED (0 MONTHS) | TREATED (12 MONTHS) | UNTREATED (0 MONTHS) | UNTREATED (12 MONTHS) | NORMAL CONTROL (0 MONTHS) | NORMAL CONTROL (12 MONTHS) |
|---|---|---|---|---|---|---|
| Peak Torque Mean (sd) / Nm | 47.42 (38.2) | 60.28 (27.58) | 52.22 (24.91) | 54.33 (29.55) | 54.75 (16.59) | 51 (17.70) |
| Mean diff | 12.89 | | 2.11 | | -3.75 | |
| t – test | **p = 0.038** | | p = 0.523 | | p = 0.975 | |
| | | | | | | |
| Impulse Torque/ Nms | 782 (713.8) | 1015.14 (534.14) | 834.22 (396.95) | 875 (486.11) | 892.3 (324.43) | 871.56 (298.70) |
| Mean diff | 233.1 | | 40.78 | | 20.82 | |
| t – test | **p = 0.0270** | | P = 0.4800 | | p = 0.5680 | |

**Table 23 Peak torque and impulse torque**

The table lists the values of peak torque/Newton metre and impulse torque/Newton metre second, during the final push in all three groups. The values were compared at the start of the treatment with those at the end of the year study. Only the treatment group showed a statistically significant increase in peak and impulse torque, both with a p-value < 0.05.

The treated group showed the only significant rise in peak torque in the final thrust following the previous ten fatigue inducing pushes with a p-value of 0.038 (see Table 23). The difference in the groups is further illustrated by the bar chart below (Fig. 79) which shows the mean values of peak torque in each subject group, both at the start and end of the year trial. The y-axis values are measured in Newton metres.

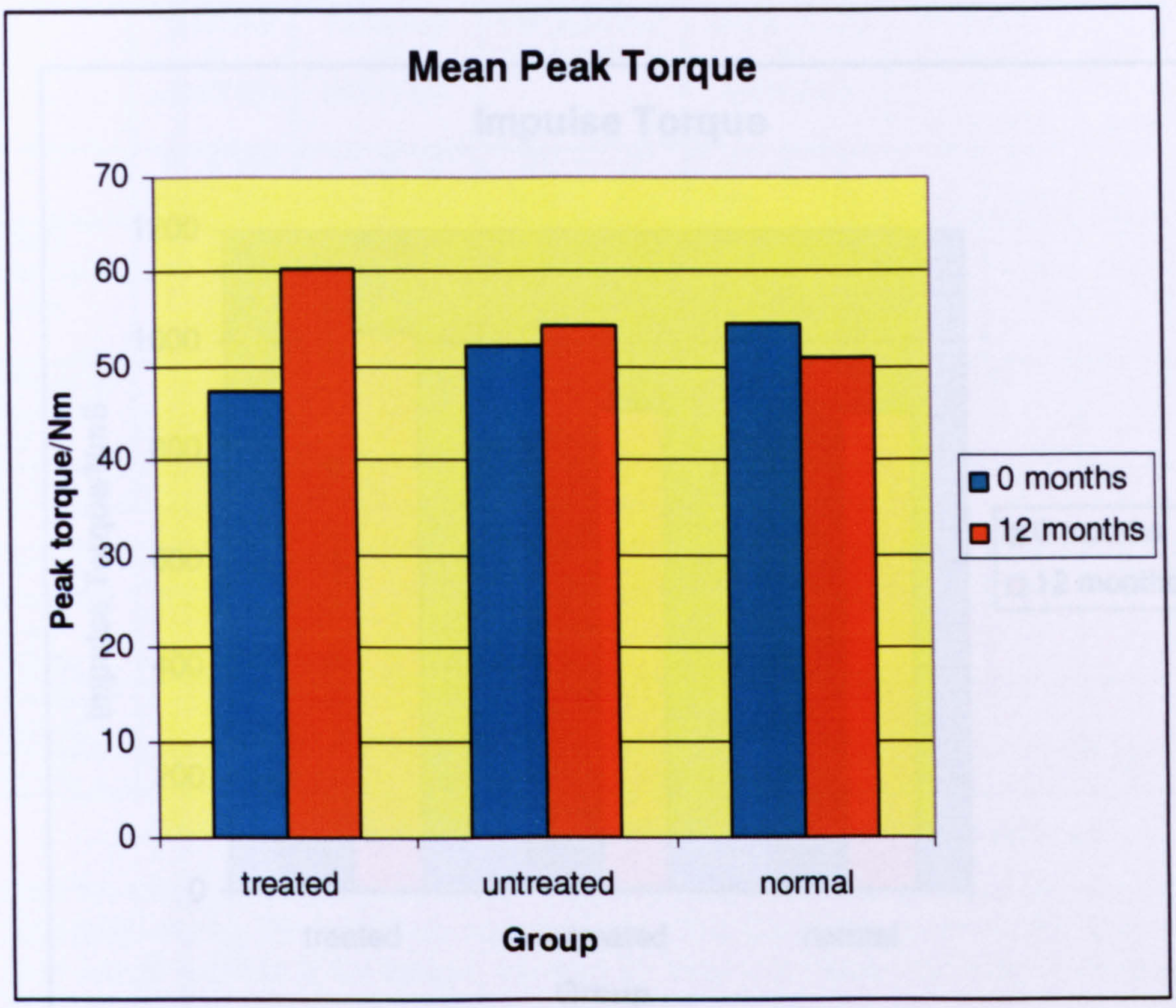



**Figure 79 Bar chart showing change in mean peak torque**

The bars in the above chart show the mean values of peak torque in each subject group, both at the start and end of the year trial. The peak torque measured was calculated from the distance of the pressure pad from the centre of the transducer multiplied by the maximum force produced in the final push when the subject was instructed to push as hard as possible. The y-axis values are measured in Newton metres.

The comparison of the mean values of impulse torque in each subject group as shown in Table 23 demonstrates a significant increase in the treated group $p = 0.0270$. This difference is further illustrated by bar chart below (Fig. 80), both at the start and end of the year trial. The impulse torque is a calculation of the area under the graph torque v time (Fig. 9) the y-axis values are measured in Newton- metres-secs.

The significant increase in the peak torque and impulse torque illustrates an improved ability to produce a force in muscles following treatment.

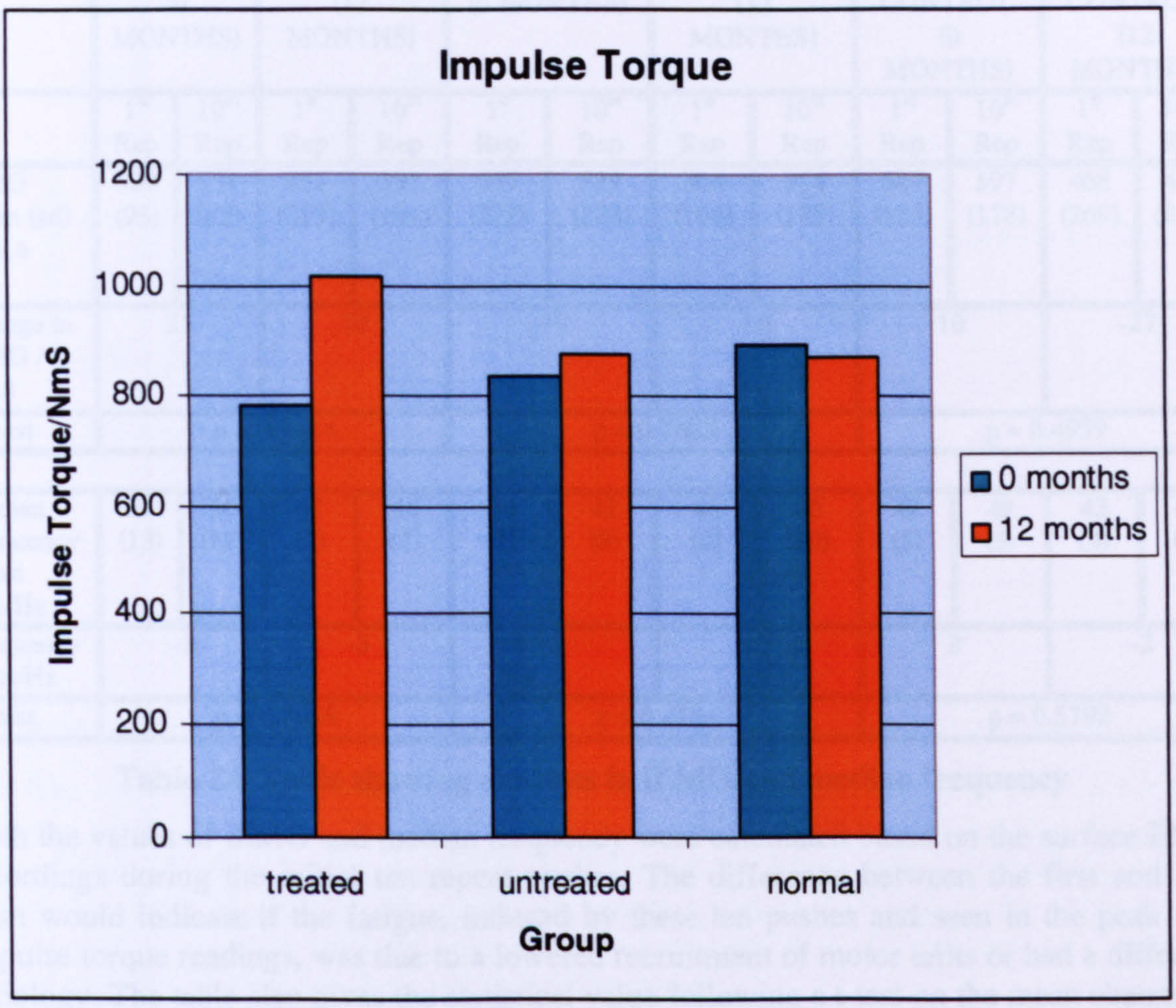



**Figure 80 Chart showing change in impulse torque**

The bars show the mean values of impulse torque in each subject group, both at the start and end of the year trial. The impulse torque measured was calculated from the distance of the pressure pad from the centre of the transducer multiplied by the mean force produced in the final push over the first 20 secs. when the subject was instructed to push as hard as possible. The impulse torque is thus a calculation of the area under the graph torque v time (Fig. 9) the y-axis values are measured in Newton- metres-secs.

## 4.4.2 Electromyography (EMG)

Table 24 presents the results for iEMG and frequency data at the start and end of the routine of 10 pushes for 20 secs., each with 10 secs. rest between.

| | TREATED (0 MONTHS) | | TREATED (12 MONTHS) | | UNTREATED (0 MONTHS) | | UNTREATED (12 MONTHS) | | NORMAL CONTROL (0 MONTHS) | | NORMAL CONTROL (12 MONTHS) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1st Rep | 10th Rep | 1st Rep | 10th Rep | 1st Rep | 10th Rep | 1st Rep | 10th Rep | 1st Rep | 10th Rep | 1st Rep | 10th Rep |
| iEMG Mean (sd) / μV.s | 530 (95) | 551 (82) | 551 (219) | 591 (191) | 539 (272) | 529 (278) | 304 (190) | 314 (172) | 587 (135) | 597 (178) | 468 (269) | 440 (240) |
| Change in iEMG / μV.s | 21 | | 40 | | -10 | | 10 | | 10 | | -27 | |
| t – test | p = 0.9624 | | | | p = 0.7483 | | | | p = 0.4959 | | | |
| | | | | | | | | | | | | |
| Median Frequency Mean (sd)/Hz | 57 (13) | 56 (12) | 47 (7) | 44 (7) | 44 (7) | 42 (8) | 46 (8) | 40 (10) | 47 (5) | 49 (5) | 43 (4) | 41 (5) |
| Frequency Shift/Hz | -1 | | -3 | | -2 | | -7 | | 2 | | -2 | |
| t – test | p = 0.3058 | | | | p = 0.4184 | | | | p = 0.5792 | | | |

**Table 24 Table showing changes in iEMG and median frequency**

Both the values of iEMG and median frequency were calculated based on the surface EMG recordings during the initial ten repeat pushes. The difference between the first and last push would indicate if the fatigue, induced by these ten pushes and seen in the peak and impulse torque readings, was due to a lowered recruitment of motor units or had a different aetiology. The table also gives the statistical value following a t-test on the mean change of iEMG and median frequency, where a p-value of $<0.05$ statistically demonstrates a significant change in motor unit recruitment.

### 4.4.2.1 The integrated EMG

As previously mentioned in section 4.3.2, integrated EMG (iEMG) refers to the area under the full rectified enveloped EMG trace (see Fig. 75). The results of the iEMG, measured in micro-Volt seconds, are shown in Table 24. These demonstrate no significant difference ($p>0.05$) in the treated patient group (column 1 and 2) untreated patient group (column 3 and 4) or the normal control group (column 5 and 6) over the year (see Table 24). This would indicate that a similar number of motor units were being recruited by all subjects during exercise at the beginning and end of the year. The results are graphically demonstrated in the bar chart below (Fig. 81).

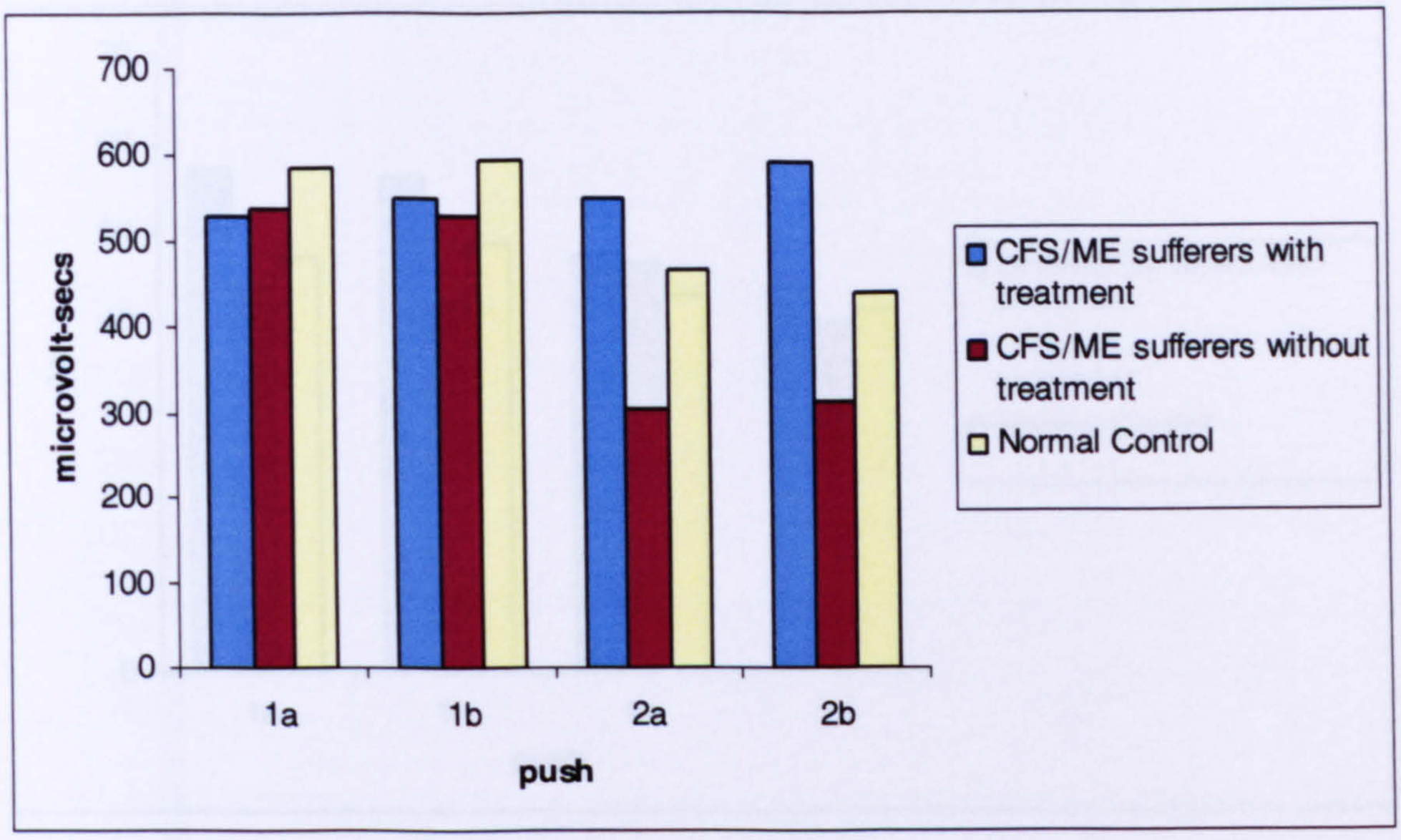



**Figure 81 Mean iEMG / μV.s of right rectus femoris before and after year of trial**

The bars show the mean values of integrated EMG in each subject group, both at the start and end of the year trial. The iEMG measured was calculated from the area under the microvoltage X time graph produced in the rectified EMG signal during the fatigue inducing, ten pre-test pushes. Where: 1a = 1st pre-test push at start of year, 1b = 10th pre-test push at start of year, 2a = 1st pre-test push at end of year, 2b = 10th pre-test push at end of year. The y-axis values are measured in microvolt-secs.

### 4.4.2.2 Median frequency

The median frequency (table 24 and Fig. 82), measured in units of Hz, from the 1st and 10th repetitive push was significantly no different in the treated patient group (column 1 and 2), untreated patient group (column 3 and 4) and the normal control group (column 5 and 6) over the year (table 24). This indicates that all subjects were fatiguing by the same amount during the exercise at the beginning and end of the year.

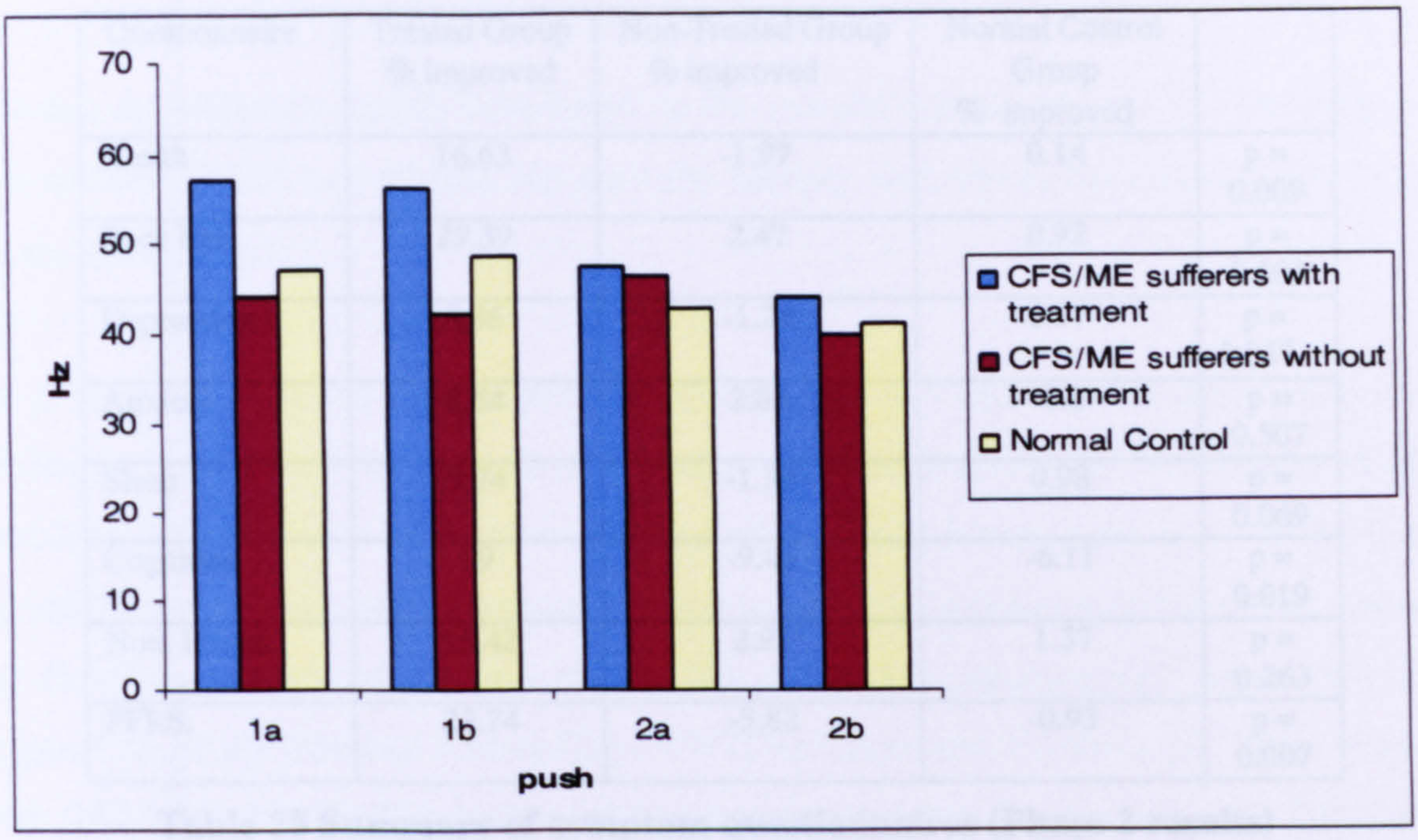



**Figure 82 Median frequency/ Hz of right rectus femoris before and after year of trial**

The bar chart show the mean values of the median frequency in each subject group, both at the start and end of the year trial. The frequency measured the number of activated motor units which decline in muscle fatigue. The median frequency of the amplitude versus frequency graph was calculated for the first and tenth pre-test pushes. Where: 1a = $1^{st}$ pre-test push at start of year, 1b = $10^{th}$ pre-test push at start of year, 2a = $1^{st}$ pre-test push at end of year, 2b = $10^{th}$ pre-test push at end of year. The y-axis values are measured in Hertz.

## 4.4.3 Symptoms

Table 25 lists the scores obtained for the symptom questionnaires, expressed in overall mean percentage change relative to the maximum score possible. In the right hand column is shown the significance factor of each questionnaire result. The result is significant if $p<0.05$. This table summarises the detailed questionnaire results reported in the previous chapter.

As stated in chapter three, significant reductions in most symptoms, notably fatigue (PFRS), pain and cognitive function were reported to result from treatment of the CFS/ME group. However the symptoms of depression, anxiety and symptoms such as insomnia were not significantly reduced following treatment.

| Questionnaire | Treated Group % improved | Non-Treated Group % improved | Normal Control Group % improved | |
|---|---|---|---|---|
| Health | 16.63 | -1.99 | 0.14 | p = 0.009 |
| Back Pain | 29.39 | 2.47 | 0.92 | p = 0.002 |
| Depression | 8.86 | -1.24 | 0.17 | p = 0.057 |
| Anxiety | 8.64 | 2.83 | -0.8 | p = 0.507 |
| Sleep | 9.74 | -1.39 | 0.98 | p = 0.069 |
| Cognition | 19 | -9.45 | -6.11 | p = 0.019 |
| Nott. Health | 15.42 | 2.92 | 1.37 | p = 0.263 |
| PFRS. | 23.74 | -5.82 | -0.93 | p = 0.007 |

**Table 25 Summary of symptom questionnaires (Phase 2 results)**

The values listed above are the differences between the mean percentage scores at the beginning and end of phase 2, where 0% = symptom free and 100% was maximum severity possible. The improvement in the treated group compared with the control groups is seen in the higher scores in the 2nd column. Note that a –ve value = a worsening in the symptoms over the year. Kruskal-Wallis nonparametric one-way analysis of variance was used to test for significant differences in questionnaire responses, as percentages of maximum scores possible, between the three groups. The final column shows the p-value which determines the statistical significance of the improvement in the symptoms of the treated group compared with the controls (See Appendix A10).

## 4.5 Discussion

There was no significant difference in the iEMG and median frequency shift between any of the three groups at the beginning and end of the pre-fatigue-exercises of 10 pushes at 33% of maximum, each for 20 seconds. Furthermore, there was no change in these values between the beginning and end of the maximal push. Therefore, it was concluded that the level of fatigue was the same in the two visits. However, the isometric results showed that only the treated patients improved in the peak and impulse torque for the final maximal push. It could be argued that the controlled exercise protocol of 10 repetitions at 33% of maximal did not induce a fatigued state. Yet, the final maximal contraction did produce a greater impulse torque at the end of the year, indicating significant improvements in the performance of the quadriceps in the treated patients, with no change in those who had no treatment.

Note that the isometric results were based on the calculations of only 7 of the treated group. Two subjects (RV01 and RV10) did not fully comply with the inclusion/exclusion criteria and are disregarded.

The process that reduces muscle strength in CFS/ME is a matter of debate. The primary philosophy behind the effectiveness of the treatment used in this study is that the prescribed manual treatment increases blood and lymph flow. Articulatory techniques of the thorax and soft tissue plus cranial techniques are all designed to improve respiratory mechanisms and fluid movement within the body. This leads to consequential improvement in oxygenation of the diseased tissues (Lay, 1997; Upledger and Vredevoogd, 1983; Magoun 1966; Still 1899, 1902). The success of the treatment implies that the fatigue in CFS/ME is possibly due to reduced blood flow, oxygenation and/or lymph drainage.

Merton *et al.*, (1973) proposed that impaired blood flow leads to a reduced oxygen supply to a muscle resulting in fatigue. It has long been accepted that the rate of blood flow through contracted skeletal muscle has an important bearing on myochemistry, and is a factor leading to fatigue (Barcroft and Millen, 1939). Earlier research has scientifically validated the use of massage to improve circulation (Goats, 1994). Point massage produced a vasotropic effect in patients suffering from vertebrobasilar insufficiency and trans-ischemic attacks and has improved the prognosis in these patients (Gusarova *et al.*, 1998). Infant circulation was also improved with a regime of soft tissue massage (Gupta *et al.*, 2002). Morhenn (2000) postulated that massage stimulates the release of the neurotransmitter substance P leading to vasodilation in the local tissues. In more recent studies human muscle fatigue has been shown to increase following physiological reductions in perfusion pressure. On the other hand Wright *et al.*, (1999) showed that although there is a reduction of blood flow in the muscle of the extremities, at the same time there is an increase in the body's central blood pressure which may partially offset the waning muscle performance.

The main purpose of the soft tissue massage used in this study was to increase blood flow in the paravertebral muscles and improve upper thoracic mobility. The intention was to subsequently stimulate the central lymphatic drainage towards the subclavian veins. The replies to the questionnaires and isometric test results indicated that the cognitive and physical functions of the treated patients were significantly improved. As this is not a double blind study, placebo could not be ruled out, though the psychological elements of CSF/ME which should have all responded well to placebo, showed no statistically significant improvements at the end of this part of the study. This indicates that there are physical or physiological changes being made as a result of the osteopathic approach, which may or may not be due to improvement of blood flow and subsequent oxygenation of tissues. A prior study by Wong *et al.*, (1992) on patients with CFS/ME has demonstrated that the reduced capacity for dynamic exercise is also associated with reaching exhaustion much more rapidly than normal subjects, at which point these patients had reduced intracellular concentrations of ATP. This latter study concluded that there was a defect in oxidative metabolism with a resultant acceleration of glycolysis in the working skeletal muscles of a CFS/ME sufferer. Oxidative stress has also been detected in CFS/ME which is damaging to DNA and lipids, leading to fatigue (Fulle, 2000). Some recent research has also shown that increased oxidative stress and decreased antioxidant defences are related to the extent of symptomatology in CFS/ME (Vecchiet *et al.*, 2003).

The idea of impaired oxygen delivery causing the fatigue associated with CFS/ME has been further explored. Oxidative metabolism and oxygen delivery was shown to be reduced in patients with CFS/ME (McCully and Natelson, 1999). Conversely, McCully *et al.*, (2003) investigated the association of CFS/ME with reduced blood flow and oxidative delivery to skeletal muscle. Muscle blood flow was measured with Doppler ultrasound after cuff ischaemia and exercise. Muscle oxygen delivery was measured as the rate of post-exercise and post-ischemic oxygen-haem re-saturation using continuous wavelength near-IR spectroscopy. Muscle metabolism was measured using (31)P magnetic resonance spectroscopy. No significant difference was noted in the patient and control groups. McCully and co-workers (2003) concluded that CFS/ME patients showed no deficit in blood flow or oxidative metabolism.

This does not mean that the observed increase in muscle performance may not occur due to an improved cardiovascular system. Aerobic exercise programmes have indeed been shown to raise blood supply plus enhance the oxygen intake and supply to tissues (Gan *et al.*, 2003; Hautala *et al.*, 2003; Valim *et al.*, 2003; Magosso and Ursino, 2002; Irvin, 1996). Nevertheless, if motor nerve dysfunction and reduction of blood flow are not the cause for the weakness, then one only has to look at the lymphatic drainage capabilities to find a highly plausible reason for the functional impairment of the muscle.

Clinical examination through palpitation in all the 18 CFS/ME patients in this study revealed engorged lymphatic vessels in the cervical and thoracic regions. This suggests that there is impaired central drainage (Kinmonth, 1960). Oedematous changes in muscles undergoing sustained low-level isometric contractions have been implicated as a major cause of fatigue (Sjogaard and Bonde-Peterson, 1981). One of the main reasons for this oedema could be the lack of adequate lymphatic drainage. The techniques of massage and manipulation employed on the patients in this study were specifically used to encourage movement of bodily fluids, (including lymph drainage), eliminate dysfunction in the motion of the tissues, relax muscular tension and release compressed bones and joints (Still, 1902; Stoddard, 1982). Kurz and co-workers (1981) have shown that histamine and serotonin were released from oedematous tissue following manual lymphatic drainage and that circulation was improved through increased output of adrenaline and noradrenalin. The improvement of central lymph drainage following the manual treatment advocated by the author has been shown to aid the intra muscular lymphatics and subsequently reduce fatigue (Bringezu, 1994).

The main drainage vessel of the lymphatics contains smooth muscle walls controlled by sympathetic nerves (Browse, 1968). Dysfunction of sympathetic control of the thoracic duct may lead to a reflux of toxins in the resultant retrograde lymph flow causing varicose lymphatic vessels predominantly in the abdomen, neck and chest (see Figs. 88-92). It may also affect the flow of CSF into the lymphatics (Kinmonth, 1960; 1982). Disturbance of normal sympathetic control, as seen in CFS/ME, offers a possible explanation regarding the

reduced muscle function seen in this study. Spinal manipulation has been well documented as a method to improve afferent and efferent sympathetic activity (Korr, 1978) and, in this instance, may aid the symptoms associated with CFS/ME.

It should be noted that in the present study, the improvement in function in the quadriceps was not achieved by any direct treatment on the lower extremity, or by any exercise regime to improve muscle strength. In fact subjects were explicitly instructed not to embark on any exercise routine during the year of study. The results showed improved peak and impulse torque which is a direct measure of the ability of muscles to produce and maintain torque. This demonstrates that there was a significant improvement in muscle function following treatment.

# Chapter 5

# 5 General discussion

## 5.1 The aetiological stages of CFS/ME: A new theory

Three predominant concepts have surfaced from the present clinical trials performed on CFS/ME patients as described in the preceding chapters. Firstly, it has been observed that muscle fatigue is of a functional nature rather than any recognisable untreatable myopathology. As shown in section 4.5 the isometric results showed that only the treated patients improved in the peak and impulse torque for the final maximal push at the end of the year . However, there was no significant difference in the iEMG and median frequency shift between any of the three groups at the beginning and end of the pre-fatigue-exercises with no significant change in these values between the beginning and end of the maximal push indicating the fatigue is induced extrinsically rather than due to an intrinsic disease within the motor unit.

Secondly, as concluded following detailed MRI scanning, CFS/ME most commonly exists in patients with no detectable pathological structural abnormality in the central nervous system. As noted in section 3.4.2.1 comparison of the proportionate CSF volume between the 3 subject groups at the beginning of the study showed no significant difference between either of the CFS/ME patient groups or the control group. Also in section 3.4.2.2, the groups showed low levels of WMH with no evidence of WMH in the basal ganglia or infratentorial structures in any patient with CFS/ME.

However there is much evidence in the preceding chapters to support the hypothesis that this disorder is a dysfunctional condition, possibly due to neurotoxic overload affecting the sympathetic nervous system brought about by a disturbance of normal lymphatic drainage of the neuraxis.

Thirdly, when examining the scientific rationale behind the treatment programme developed by the author, which has been shown to reduce the symptoms of CFS/ME, it

seems likely that the muscular and cerebral symptoms are linked by the pathophysiological process discussed in sections 2.5; 3.5 and 4.5. As stated in this thesis, long lasting hyperactivity of innervating sympathetic pathways seems to be a prevailing theme in many clinical conditions, involving various organs and tissues (Korr, 1978). Sympathetic nerve control of smooth muscle walls causes pulsatile contractions in thoracic duct aided by valves along its structure which maintain unidirectional flow (Kinmonth, 1982). Dysfunction of sympathetic control of the thoracic duct leads to a reflux of toxins in the resultant retrograde lymph flow causing varicose lymphatic vessels predominantly in the abdomen, neck and chest (Kinmonth, 1982; 1960). This further reduces flow of CSF into the lymphatics (Knopf and Cserr, 1995). The afferent sympathetic outflow, in particular, may be modified by the treatment developed by the author.

Drawing on all the information detailed in the first four chapters with careful consideration of the clinical findings, the author has formulated a theoretical model to explain the aetiology, symptoms and the rationale behind a novel treatment regime for CFS/ME. This treatment programme was developed over the past fifteen years involving manual lymphatic drainage and soft tissue massage of primarily the upper thoracic, cervical and cranial regions. The osteopathic approach does not set out to directly eliminate toxins from the body; rather it facilitates the patient's own inbuilt mechanisms responsible for toxin elimination. By modifying afferent sympathetic tone via osteopathic treatment the symptoms of CFS/ME are diminished.

A model of the stages of development of this disease is proposed below which may be applied to all CFS/ME patients seen by the author over the past one and a half decades.

**Stage 1** Patients with CFS/ME all seem to have a predisposing history of sympathetic nervous system overload:

a. Physically by being an overachiever at work, during study or in sports. Rarely, it can be the opposite by being too sedentary (Perrin, 1993).

b. Chemically by constant exposure to environmental pollution (Rogers, 1990; Dustan *et al.*, 1995).

c. Immunologically by chronic infections or hypersensitivities to multiple allergens (Shepherd, 1998; Crook, 1984).

d. Psychologically/emotionally by family and or work related mental stress (Black, 1999 and Sharpe, 1996).

**Stage 2a** In patients with CFS/ME the lymphatic drainage of the neuraxis shows signs of being compromised in the cranium, mostly in the cribriform plate region of the ethmoid bone.

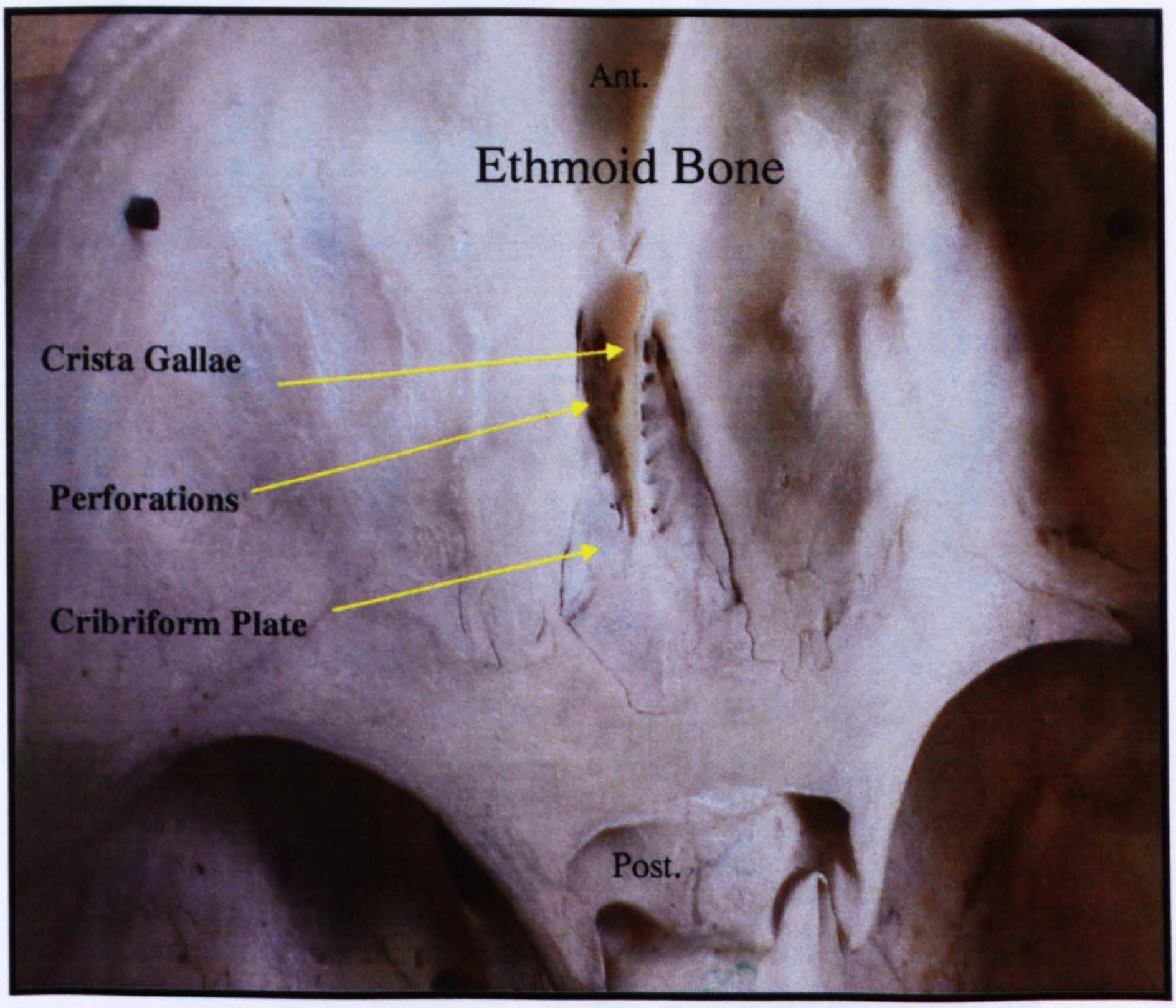



**Figure 83 Superior view of the cribriform plate with observed perforations.**

The perforations seen above allow the passage of blood vessels, nerves and cerebrospinal fluid from the cerebrum to the nasal sinuses situated directly below the ethmoid bone.

This drainage problem clinically appears to arise from a prior defect in the skull, usually in the frontal/nasal region due to either a congenital, hereditary or traumatic aetiology. This

may be exacerbated by chronic sinusitis leading to further congestion affecting the lymph channels in the mucous membranes of the nasal sinuses.

**Stage 2b** The lymphatic drainage of the neuraxis is subject to further disturbance in the spine, usually in the cervical or thoracic region, due to either a congenital, hereditary or postural defect and/or prior trauma.

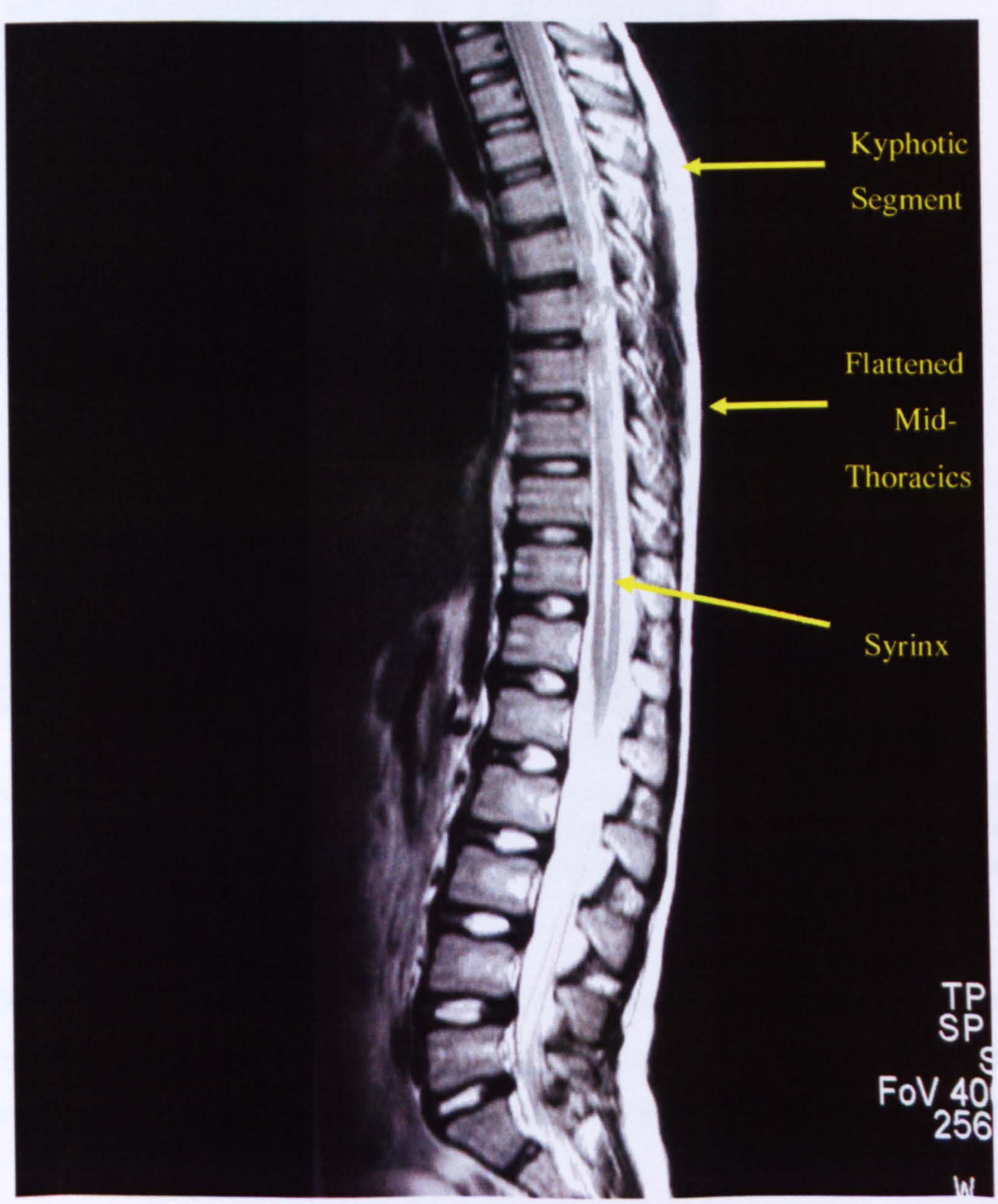
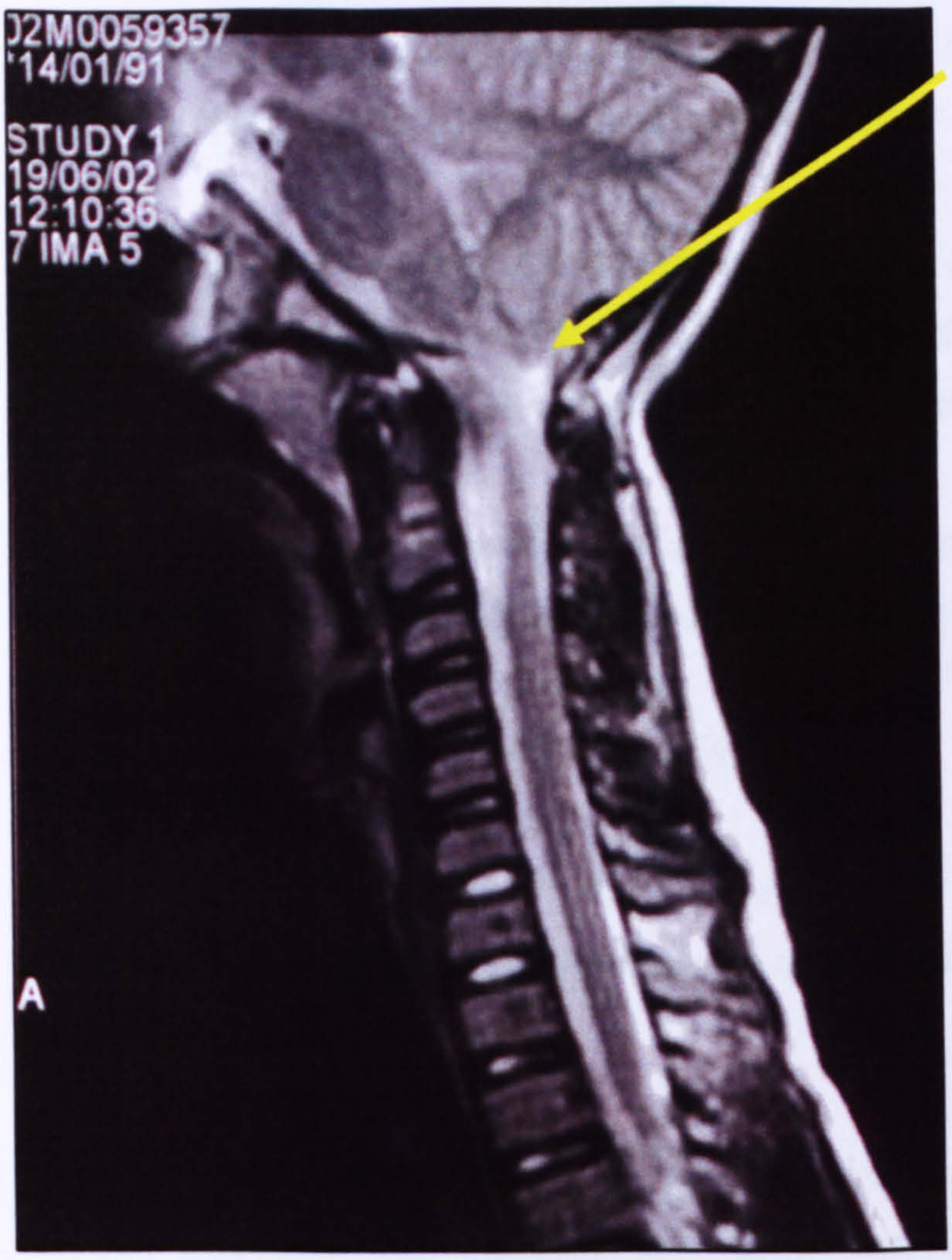



**Figure 84 MRI sagittal image showing spinal defect in 12 year old girl with CFS/ME**

The postural disturbance of the thoracic spine in most cases of CFS/ME is usually not too severe with usual evidence of old osteochondrosis with a flattened upper thoracic region. A syrinx (cyst within the spinal canal) seen in this MR image is rare but demonstrates the extent of possible spinal dysfunction.




Defect is evident when cerebellar tonsil descends into cervical spine

**Figure 85 Upper cervical defect in same 12 year old girl**

A defect at the uppermost region of the cervical spine is found in many cases of CFS/ME. The sagittal MR scan shows a partial herniation of the cerebellar tonsil into the spinal canal. (If the herniation penetrates further into the cervical region it is known as a Chiari Malformation).

**Stage 3** The chronic hyperactivity of the sympathetic nervous system will be compounded by toxic affects due to the long term dysfunction of the neuraxis drainage; this further overloads the hypothalamus and subsequently the sympathetic nervous system.

**Stage 4** A final trigger factor strikes, which usually arises from a viral infection, but may be physical or emotional in nature. As already stated in section 2.5.3.1.2 prolonged somatic dysfunction often leads to repetitive nociceptive input, a consequential overstimulation of the PGi-LC may contribute to the chronic adaptive response that ensues (Aston-Jones *et al.*,

1990). The ensuing cascade of sympathetic activity and dysfunction of fluid dynamics in the body and most importantly in the lymphatic drainage, leads to observed early symptoms of muscular fatigue and disturbance in cognitive ability.

**Stage 5** There will be a disturbance in autonomic, as well as hormonal function, as toxins in the cerebral blood flow and ventricular system directly affect control of the hypothalamus. Hormonal transport within CSF may also be directly affected by toxic overload.

**Stage 6** Dysfunction of sympathetic control of the thoracic duct leads to a reflux of toxins in the resultant retrograde lymph flow causing varicose lymphatic vessels predominantly in the abdomen, neck and chest (Kinmonth, 1982; 1960). This further reduces flow of CSF into the lymphatics (Knopf and Cserr, 1995).

**Stage 7** Further impairment of toxic drainage of the neuraxis, due to the retrograde lymphatics, results in increased hypothalamic dysfunction and an even greater reduction of lymphatic drainage.

**Stage 8** The continuing sympatheticonia results in further systemic disturbances. Somatic, visceral, emotional, immunological and environmental stressors continue to affect the damaged brain stem-hypothalamic mechanisms to increase sympathetic catecholamines and adrenal cortical hormones leading to a chronic adaptive state known as CFS/ME.

## 5.2 The physical signs of CFS/ME

The concept of CFS/ME being primarily a physical disorder is foreign to most of the medical profession. However, many of them recognise that CFS/ME has physical symptoms. There are physical components within the internationally recognised criteria that verify the diagnosis of CFS/ME. These include sore throat, tender cervical or axillary lymph nodes, myalgia, and polyarthralgia (Fukuda *et al.*, 1994). In the fifteen years since the author started to examine and treat patients with CFS/ME, repeated patterns of physical signs have emerged among sufferers that can not be dismissed as pure coincidence. All the physical phenomena seen in CFS/ME can be understood when the pathophysiology of the

disease is viewed as being neurolymphatic in origin with impaired drainage resulting in sympathetic dysfunction. The main physical signs are shown in the illustration below (Fig. 86).

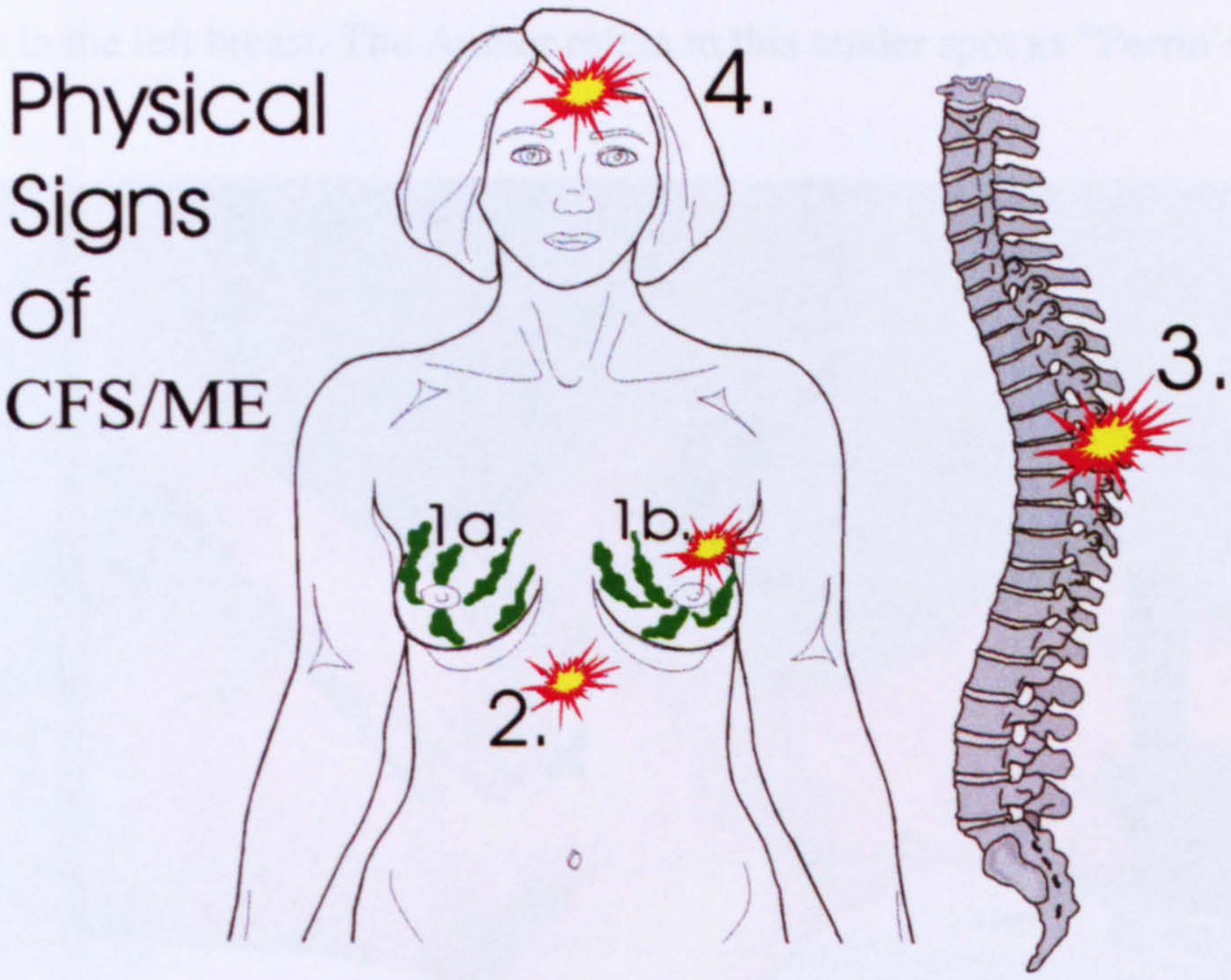



**Figure 86 The observed physical signs of CFS/ME**

These regions of tenderness or dysfunction were identified in all CFS/ME sufferers seen by the author over the last ten years in both the university and clinical settings. A full description and an explanation of the above findings are detailed below.

## 5.2.1 Varicose lymphatics and Perrin's point

In every CFS/ME patient, whether male or female, there was very tender area in the upper lateral region of the breast tissue, roughly 2cm superior and lateral to the left nipple (Fig. 87). This is the area where the pectoral muscles and lymphatic tissue overlap. This finding is significant because this tender area almost always lies on the left side and is level with

the position at which the thoracic duct turns to the left. The heart and the main blood vessels are supplied with sympathetic nerves via the cardiac plexus which has a greater concentration of nerves in the left than the right. The cardiac sympathetics, and those innervating the thoracic duct via viscero-somatic reflexes, irritate sensory nociceptors at this point in the left breast. The Author refers to this tender spot as "Perrin's Point".

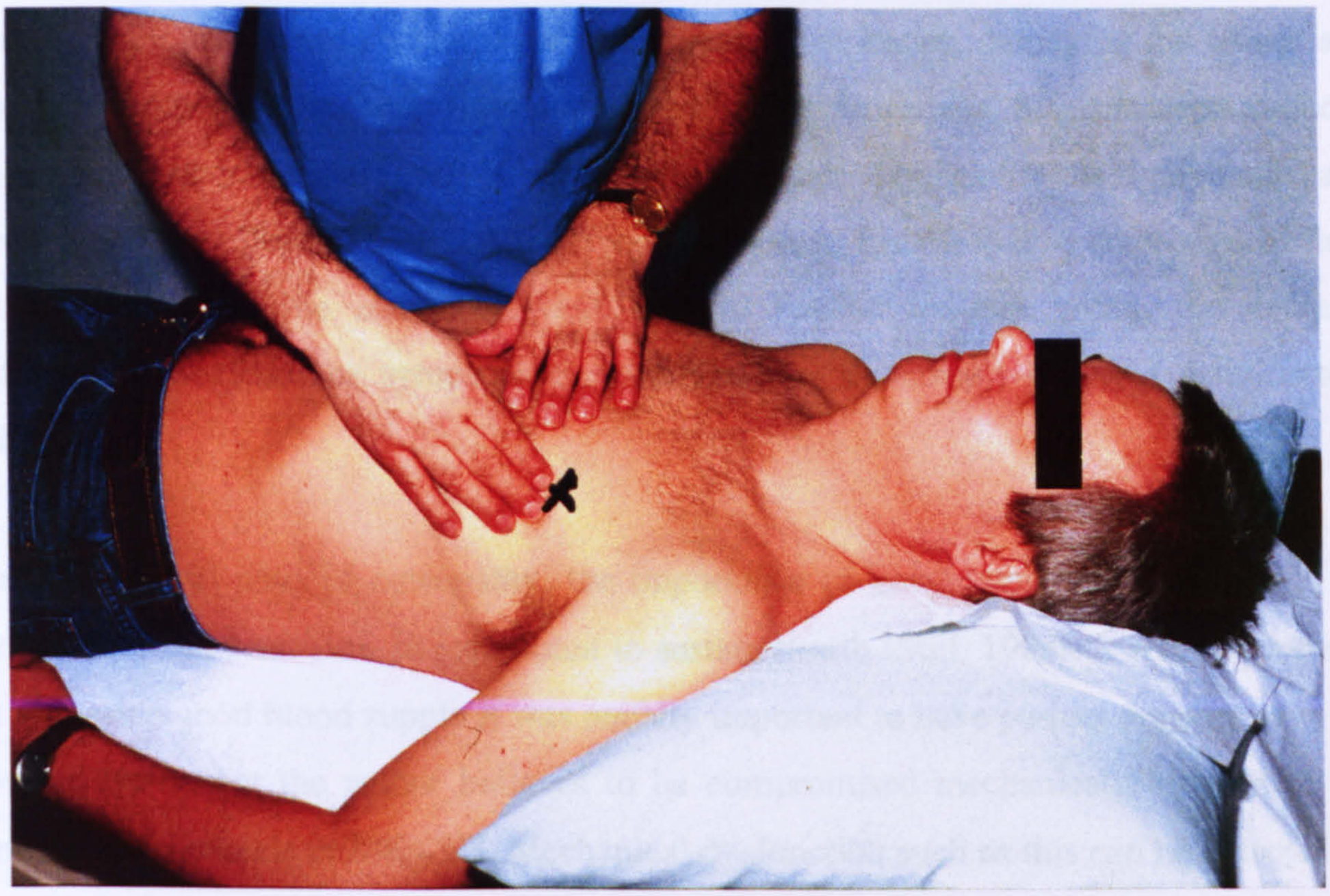


**Figure 87 Examining the patient for 'Perrin's point'**

Gentle pressure at a point slightly superior and lateral to the left nipple "Perrin's Point" (**X**). The amount of sensitivity at this point appears to correspond to the severity of lymphatic engorgement in the breast tissue and also seems to mirror the gravity of the other symptoms.

This sensitive region, together with congested lymph vessels in the cervical region and breast tissue, was palpated in all 18 CFS/ME patients in the second phase of the study. The consistency of these lymphatics can best be described as "beady" and similar to varicose veins in the leg. Varicosities have been described in the lymphatics (Kinmonth, 1960). Large incompetent varicose lymphatics known as megalymphatics have often been seen when this backflow occurs. However varicosities in the lymphatics are rarely discussed in

medical literature, purely due to the misconception that lymph flow is unidirectional due to the valvular system in the lymphatic vessels. Thus the concept of backward pressure is not generally known and the possibility of varicose lymph is rarely considered when examining lymphatic tissue. It is now established that a chylous reflux does exist (Kinmonth, 1982).

Downward pressure due to thoracic duct pump dysfunction caused by sympathetic disequilibrium may lead to a contra-flow within the lymphatics, damaging the valves and creating a pooling of lymphatic fluid with "beading" of the vessels. Stasis in these varicose lymphatics creates risk of toxic overload plus further damage to the lymphatics and surrounding tissue. Reflux of toxins via lymphatic vessels back into the cerebro-spinal fluid will further irritate the central nervous system. Further toxicity within the neuraxis continues to overload the sympathetics resulting in a downward spiral of deteriorating health.

From the earliest days of osteopathy, the importance of good lymphatic drainage in the thoracic duct has been seen as paramount to sustain health (Still, 1902). It was emphasised that alongside good blood supply it was equally important to have perfect drainage.It is the above pathway that the author believes to be compromised mechanically as part of the common pathogenesis in ME/CFS. Mechanical dysfunction such as this can be detected by palpation and can be released by gentle pressure techniques applied to the cranium and the spine.

The healthy lymphatic vessel allows only unidirectional flow due to the valvular system as diagrammatically illustrated in Fig. 88. In CFS/ME, retrograde flow of the lymphatics is produced by the reverse peristaltic wave of the thoracic duct which arises from dysfunctional sympathetic control of the duct's smooth muscle wall (Fig. 89).

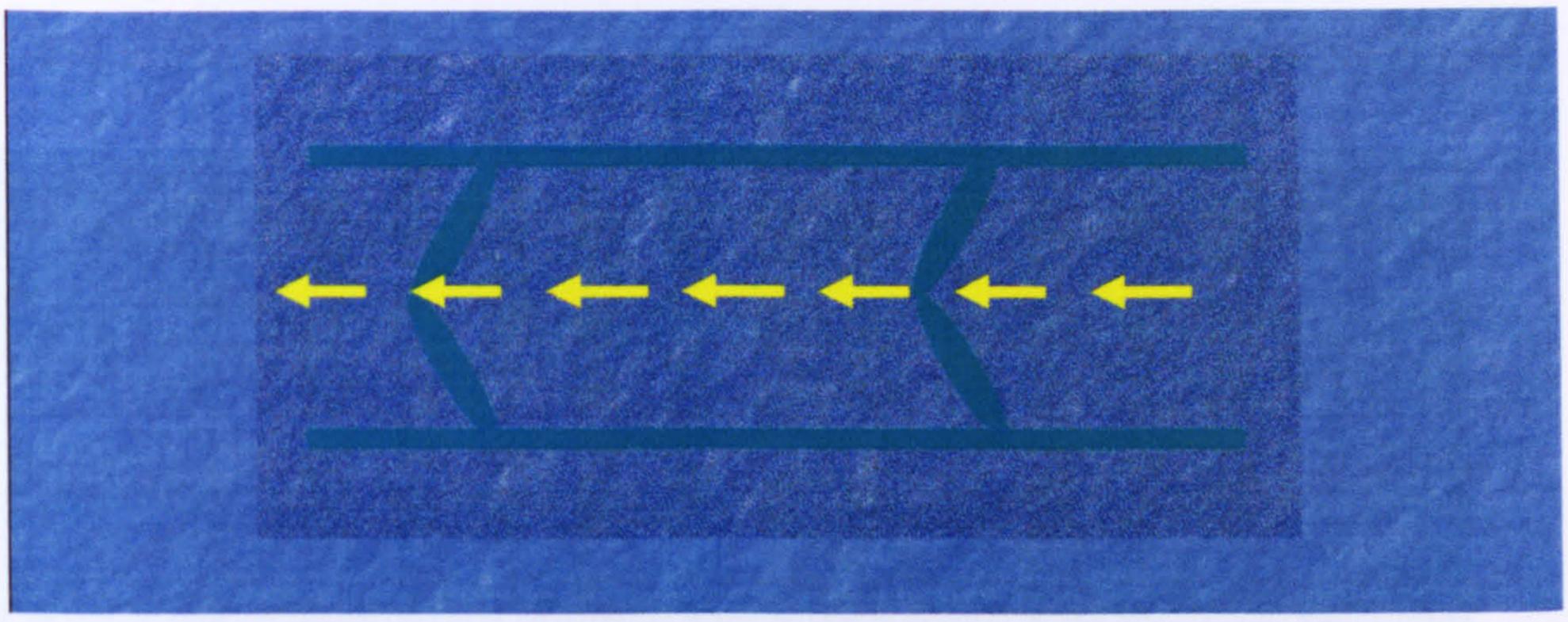


**Figure 88 Schematic showing normal flow within a healthy lymphatic vessel**

The valves in this healthy vessel are intact preventing any backflow, thus maintaining a unidirectional flow of lymphatic fluid.

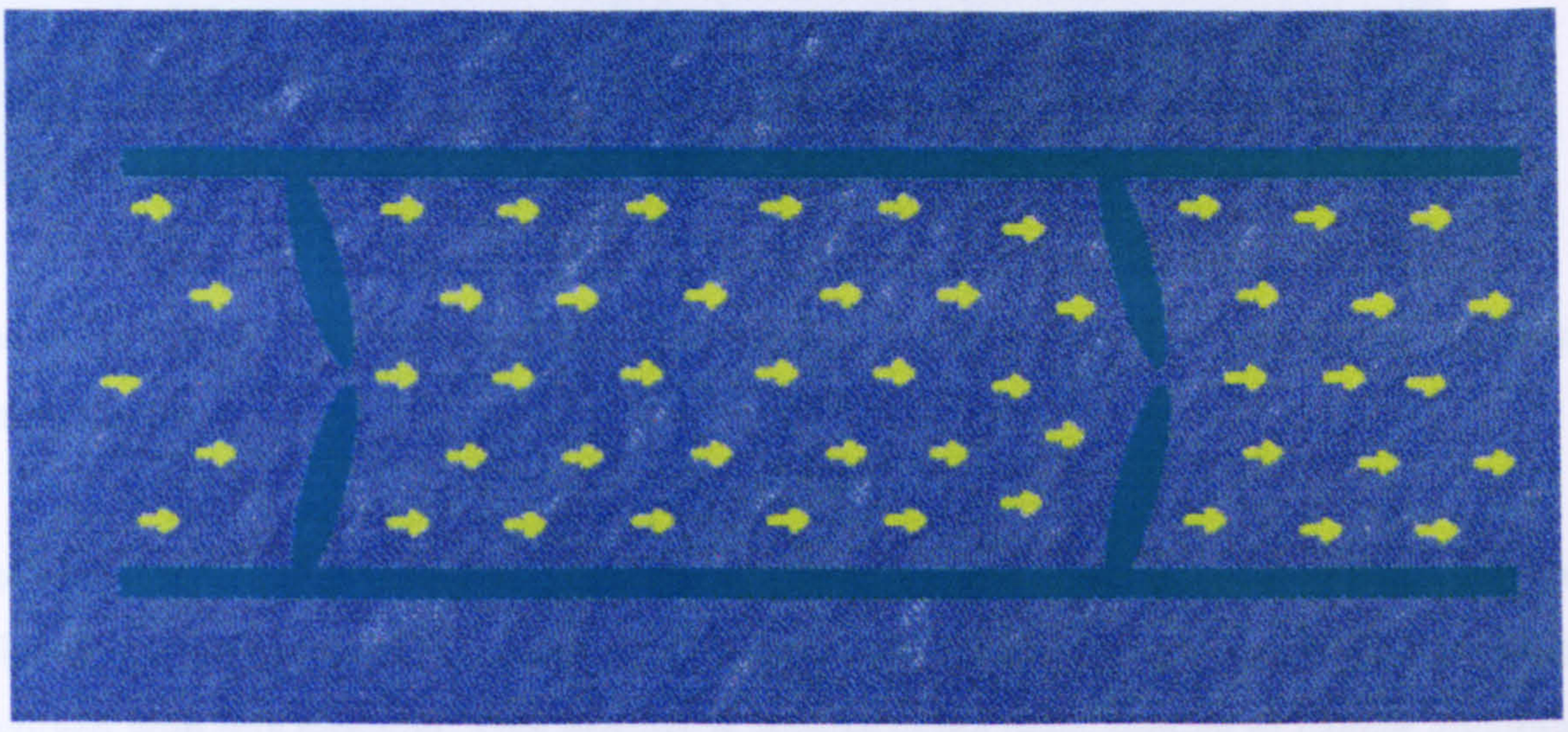


**Figure 89 Retrograde lymphatic flow**

If the normal peristalstic wave of the thoracic duct is disturbed resulting in a reflux, then the ensuing back-pressure will weaken the valves allowing a retrograde flow.

Eventually the lymphatic reflux causes damage to the valves and allows pooling of fluid in between the valves. This leads to distension of the vessel wall with the characteristic beaded appearance of a varicose vessel as illustrated in figure 90.

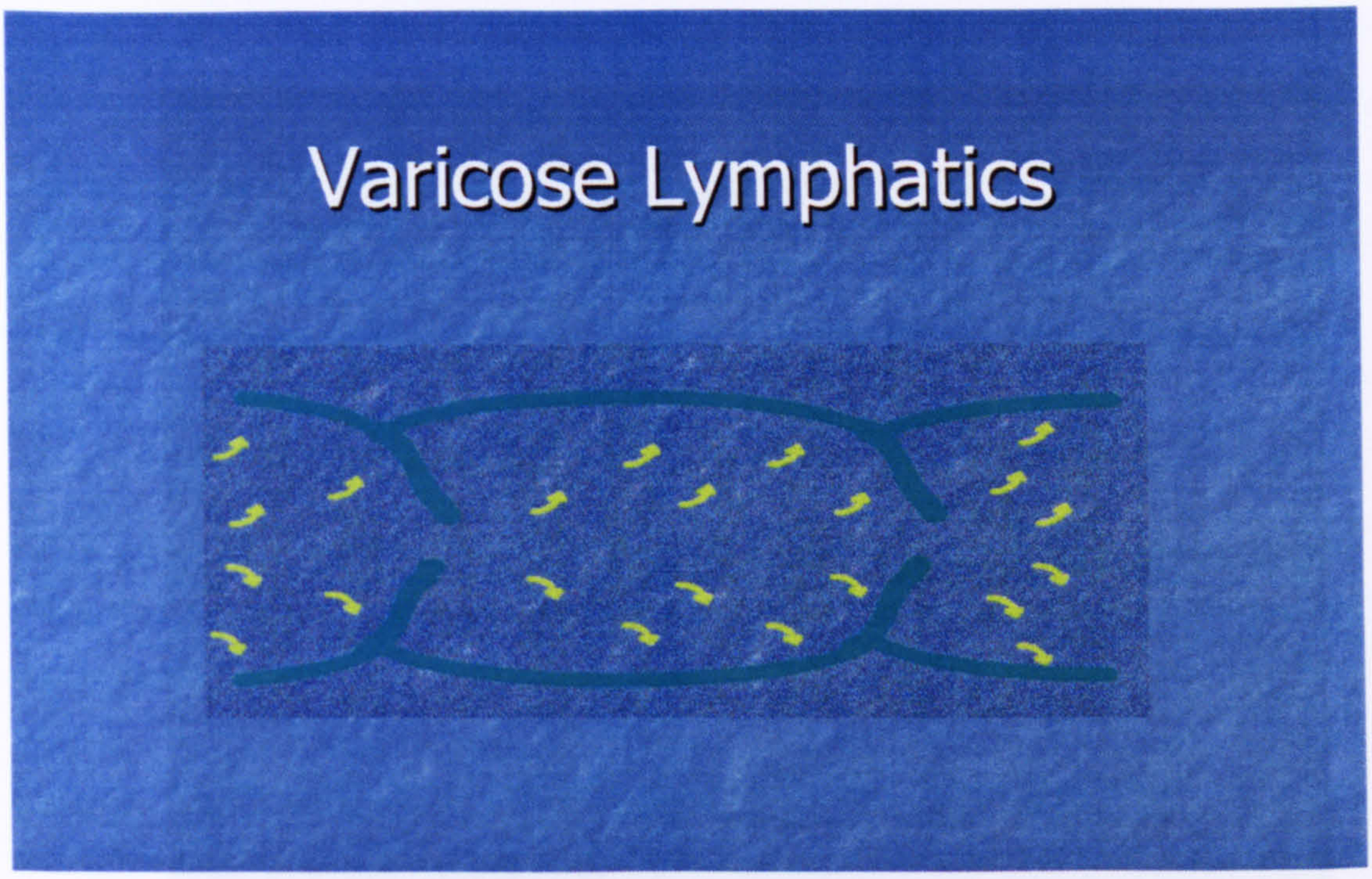



**Figure 90 Schematic showing the formation of lymphatic varicosities**

The walls between the collapsed valves become noticeably distended with further reflux of lymphatic fluid.

The above schematics (Figs. 88-90) show the development of varicose lymphatics that were palpable in the chests of all cases of CFS/ME seen by the author, including the patients involved with this research. This process is similar to the development of deeper abdominal lymphatic varicosities as seen in many lymphatic disorders (Kinmonth, 1960; 1982).

The following photographs (Figs. 91a and b) are of the chest of a 61 year old gentleman who suffered severely from CFS/ME for four years before being successfully treated with a two year course of osteopathy. For the past four years, since completion of the 2 year treatment period, he has been steadily increasing his activity and was found to be virtually symptom free when he returned for six-monthly check-ups. However, the pressure on the lymphatic system during years of illness has taken its toll on the constitution of the lymph vessel valves leaving permanently engorged varicosities. Even though he is now generally well, except after extreme exertion, he still has to regularly carry out the lymph drainage massage technique.

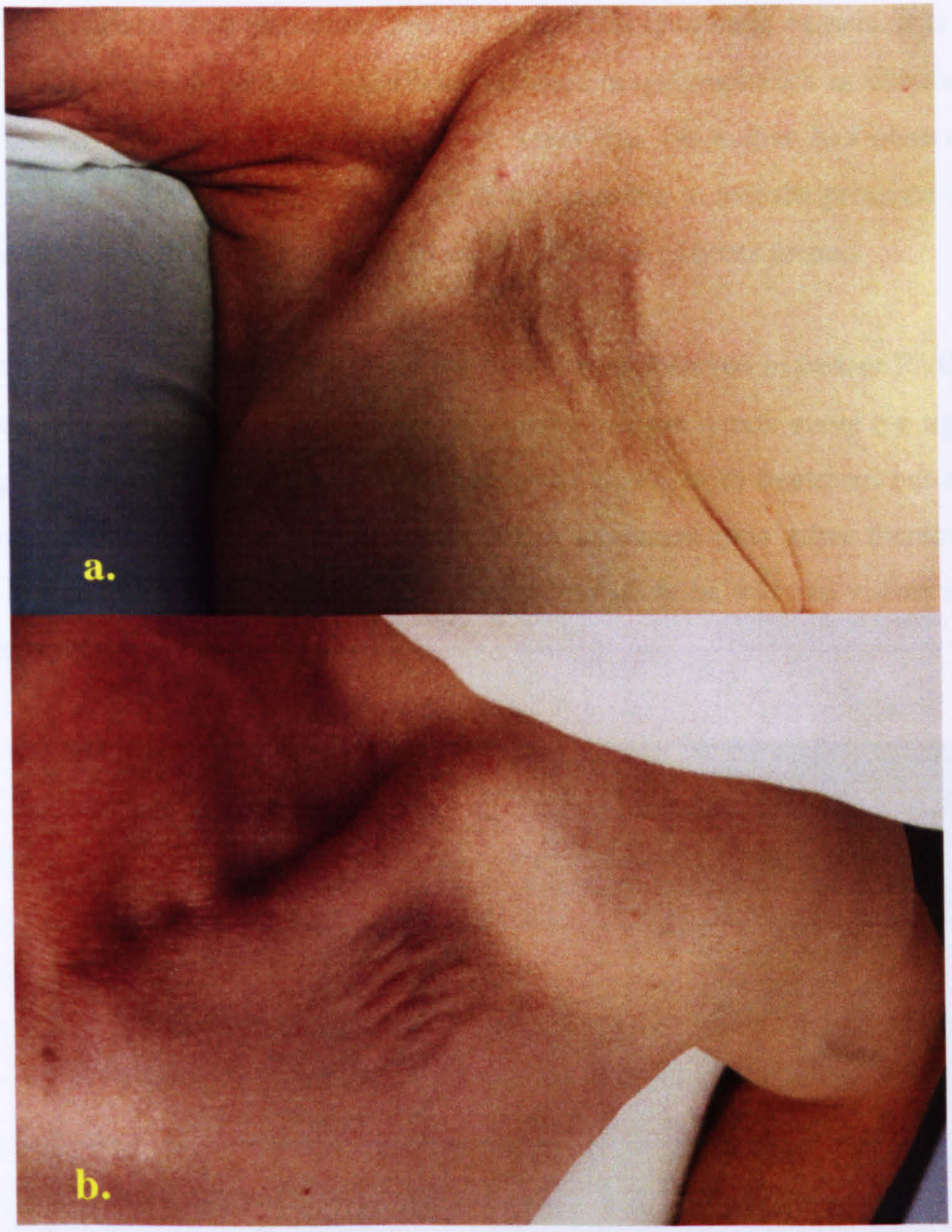



**Figure 91 Right and left subclavicular varicose lymphatics in patient with CFS/ME**

In photograph **a**, taken 4 years after completing a 2 year treatment programme, one can clearly see five separate varicose lymphatic vessels under the skin at the anterior medial aspect of the right shoulder, the central one being the most pronounced. A further example of the left subclavicular region in the same patient is seen in photograph **b,** taken six months after the first photograph, with the megalymphatics even more pronounced.

The beaded appearance in figures 91 a. and b. are due to damaged valves and subsequent retrograde flow and pooling of lymphatic fluid. This is similar to the formation of varicose veins although it lacks the darker, bluish hue of superficial varicose veins. The creamy

appearance of lymph is almost apparent in these engorged vessels which present with a much larger diameter than in normal healthy superficial lymphatic vessels. It is extremely rare to actually see such obvious superficial varicose megalymphatics as illustrated above. In fact this was one of the only times in 15 years that the author had observed such a pronounced superficial varicosity. However it was possible to feel the presence of varicose lymphatic vessels in the neck and chest of all the CFS/ME patients treated.

A third case of visible and palpable varicose lymph was observed in patient RV08 from the treated patient group of phase 2. He showed visible varicose lymph under the right clavicle following effleurage. This 22 yr old male improved slowly with treatment but after a year of treatment, he still required further osteopathic treatment plus other therapies to help detoxify him. At four years after the beginning of the study he still had visible evidence of lymphatic reflux as shown in figure 92.

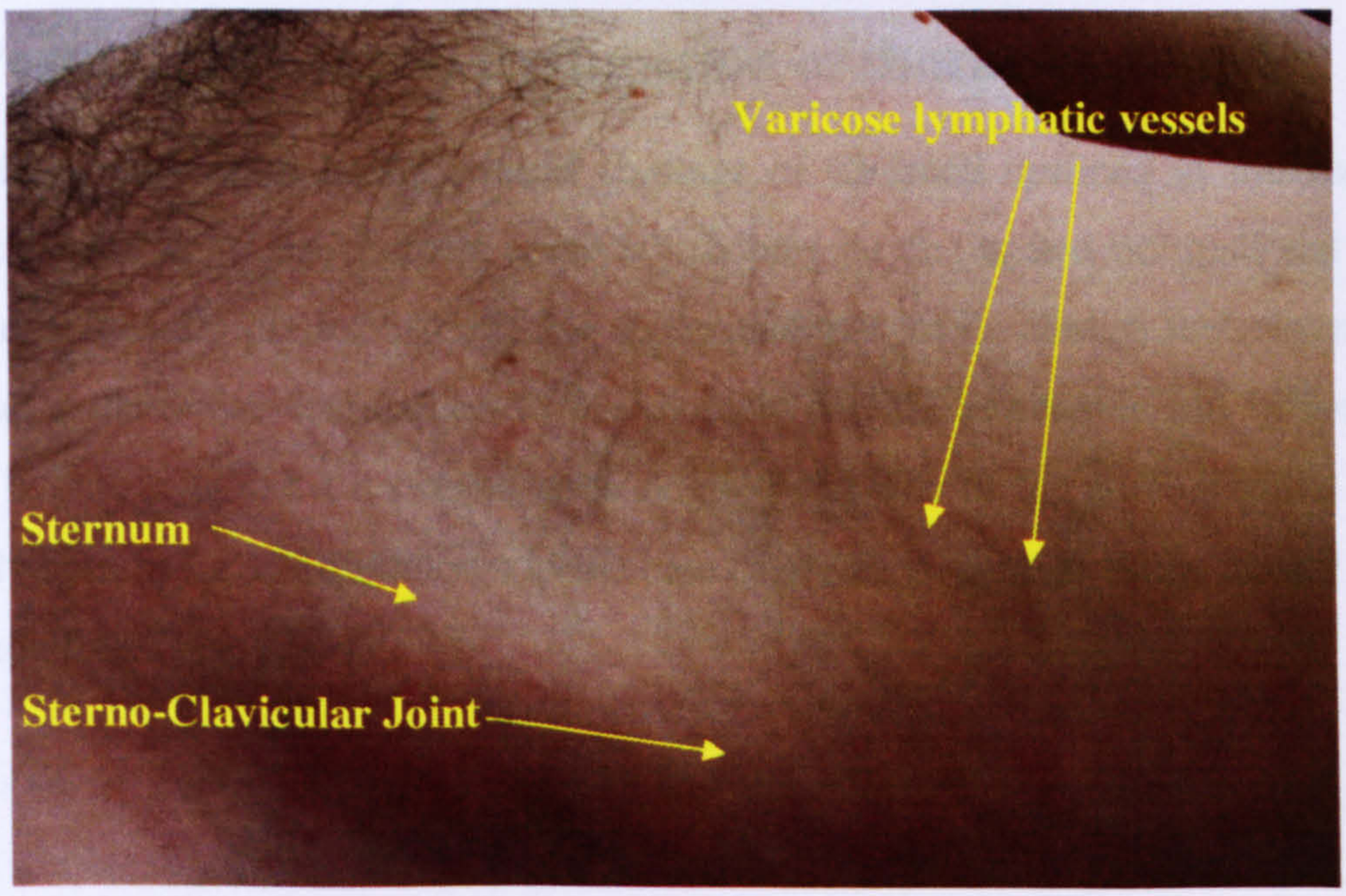



**Figure 92 Superficial lymphatic varicosities seen in research patient RV08**

The chest of a 22 year old male viewed from above the right sterno-clavicular joint showing superficial lymph vessels that are tortuous as they travel towards the right subclavian vein. Photograph taken 4 years after commencement of treatment.

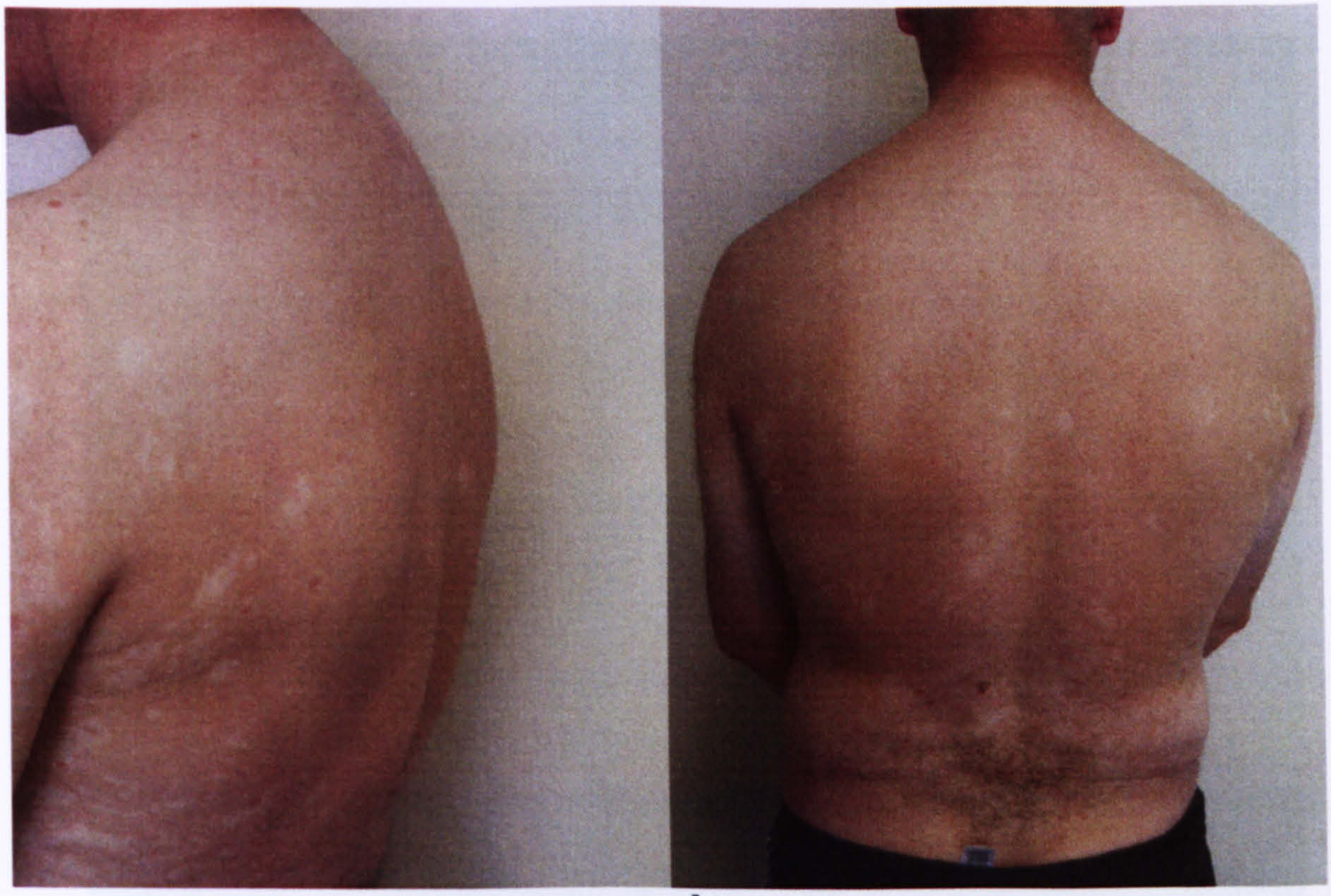
## 5.2.2 Tenderness in coeliac plexus region

The largest major autonomic plexus uniting two large coeliac ganglia is known as the coeliac plexus. This major plexus is level with the 12$^{th}$ thoracic/1$^{st}$ lumbar segment and is situated posterior to stomach and anterior to crura of diaphragm. Secondary plexuses connected to coeliac plexus are: phrenic; splenic; hepatic; left gastric; intermesenteric; suprarenal; renal; testicular/ovarian; superior mesenteric and inferior mesenteric.

Through its connections, it is excellent as an indicator for any visceral disturbances from waist down. Clinically it has been observed by the author that tenderness in the hypochondrium seems to be directly related to the severity of any lower extremity fatigue and or abdominal problem. This tenderness is most likely due to stimulation of connecting peripheral somatic nociceptive afferent fibres with sympathetic nerves observed in pathological mechanisms (Janig, 1988) see section 2.5.3.1.1.

## 5.2.3 Postural/structural dysfunction of thoracic spine

A prevailing observation in the clinical findings of CFS/ME outlined in this thesis is a mechanical disorder of the thoracic spine which may be due to bad occupational posture, congenital or genetic predisposition. All of the patients in the studies undertaken by the author had a particular dysfunction in the thoracic region, whether it was inflammation, lordosis, kyphosis or just a restricted area. A good example of the type of spinal problem commonly seen in CFS/ME is shown in the case of RV05, a member of the treated group in the second phase (Fig. 93).



**a .** **b.**

**Figure 93 Mechanical dysfunction of thoracic spine**

Lateral **a** and posterior **b** views of research patient RV05, a 53 year old married social worker. Note the kyphotic dorsal spine with a lateral curvature in dorso-lumbar region (NB the patches of vitelego have no known association with CFS/ME). See Appendix A5 for patient's previous history.

Another common structural disturbance seen by the author in CFS/ME patients was a flattening of the curvature in the mid thoracic spine, usually accompanied by the presence of a kyphotic dorso-lumbar region. An example of the defect seen is shown in the accompanying photograph (Fig. 94), which can be compared with the healthy posture as shown previously in Figs. 1C and 1D. This postural defect is often caused by the prior condition osteochondrosis or Scheurmann's disease affecting spinal development in adolescence, which may have occurred years before onset of the distinct symptoms of CFS/ME.


**Figure 94 Flattening in upper thoracic spine with signs of previous osteochondrosis**

Female, 43 year old journalist who has been retired for 4 years due to ill health, Married with no children. She had a tonsillectomy when 7 y.o.a.; and chronic migraine. Eight years prior to consultation she suffered concussion after hitting top of head.

## 5.2.4 Change in regular cranio-sacral rhythm

As described in section 2.2.4.6, there is a palpable rhythmic pulsation along the spinal cord and around the brain together with that of normal breathing, which is transmitted to the rest of the body and is termed the involuntary mechanism, cranial rhythmic impulse (CRI) or the "cranio-sacral rhythm". Most of the osteopathic profession believe the pulse to be a movement through the tension and continuity of membranes, dura and fascia. The fascia is continuous with the membranes that surround the brain and spinal cord, the meninges, thus allowing the different motions, and tensions, of the body to be transmitted everywhere. Sutherland proposed that the inherent, involuntary cycle of mobility of the cranial bones

and also that of the sacrum between the ilea corresponds with the motility of the neural tube and fluctuation in the flow of the cerebrospinal fluid (Sutherland, 1990).

Sutherland (1990) also proposed that the primary respiratory mechanism produces a rhythmic alternation of flexion and extension of structures in the midline. This movement occurs simultaneously with rhythmic external and internal rotation of all paired lateral structures. It has also been suggested that contractile lymph tissue exists throughout the body which creates a powerful pumping mechanism (Kinmonth, 1982). It has been shown that the thoracic duct pump influences the drainage of CSF/lymph from the neuraxis. Together with the pulse rate and the effects of breathing, a separate underlying rhythm may be induced which is very possibly the aforementioned 'involuntary mechanism'. This rhythm echoes along the lymphatic system, resonating throughout the entire body and can be palpated by trained osteopaths. In CFS/ME patients it is slower and its intensity shallower than in normal subjects. This was found to be the case in all the patients in the present study.

## 5.3 Future developments

### 5.3.1 Multidiscipline comparative studies

Multicenter studies using a much larger cohort of patients are most definitely required in the future to further validate the hypothesis explored in this thesis. Also the chosen osteopathic method used in this study should be tested alongside other accepted treatments in order to gain wider acceptance.

The treatment plan developed by the author has already been independently validated by a recently published survey conducted by a local patient support group (Vernon, 2004). One hundred and fifty members of the Stockport M.E. support group answered questionnaires related to the services provided by NHS professionals and complementary practitioners. One of the outcomes of this independent survey was a list of therapies that the group's members found useful in managing their illness.

| THERAPY / TREATMENT | Number of Patients Expressing a Preference |
|---|---|
| Osteopathy – the cranial/lymphatic approach (as practicsed by Raymond Perrin (p.214 *et seq* this thesis)) | 28 |
| Nutrition/ Allergy testing | 21 |
| M.E. specialist Dr Andy Wright (who recommends many forms of new treatments that have shown to help including the author's manual approach). | 16 |
| Healing/ Reiki | 15 |
| Homeopathy | 11 |
| Remedial Yoga | 11 |
| Acupuncture | 9 |
| Meditation | 9 |
| Thyroid specialist | 8 |
| Counselling | 7 |
| Tai Chi | 6 |
| Herbalist | 6 |
| Aromatherapy | 5 |
| Massage | 3 |
| Alexander Technique | 2 |
| Bowens Technique | 2 |

**Table 26 Results of Stockport ME patients support group survey on treatment therapies effective in their case: listed in order of preference (Vernon, 2004)**

Some of the 150 patients listed more than one treatment that they had found helpful. This explains why the total of all patient numbers in this table add up to 161.

The data suggests that although aromatherapy, massage, the Alexander and the Bowens techniques are also forms of therapy with the emphasis on the physical, they score the lowest ratings in the table compared to the manual treatment advocated in this thesis which scored the highest. So the observed benefits are not achieved by the mere laying of hands by a sympathetic practitioner. The complete treatment approach developed by the author is required including spinal, cranial and specialised lymphatic drainage techniques.

## 5.3.2 Lymphatic drainage of the neuraxis and the CRI

Another area of exploration arising from this thesis that requires further investigation is the possibility that the aforementioned CRI (cranial rhythmic impulse) and the drainage of CSF into the lymphatics, echoing the thoracic duct pump, are one and the same.

Attempts have been made to explain the rhythm felt by cranial practitioners. Farasyn (1999) suggested that the intrinsic movements of cranial bones, fascia and organs may be due to local venomotion pulsation, the reflection of which we may palpate at the skin surface. However this theory is difficult to accept due to the absence of contractile tissue in the veins and sinuses of the brain. The cerebral veins are unique in that they possess no muscular tissue in their very thin walls and have no valves. Consequently any palpable venous pulsations in the head are mere remnants of larger vasometric pulsations of the inferior vena cava and iliac vein. The cerebral veins descend from the brain into the subarachnoid space by penetrating the arachnoid mater and the meningeal layer of the dura thereby draining into the cranial venous sinuses. Most significant is the cavernous nodule lying at the confluence between the great vein of Galen and the straight sinus and the Cavernous sinuses which are situated in the middle of the cranial fossa on each side of the sphenoid bone. The internal carotid artery, surrounded by its sympathetic nerve plexus runs forward through the sinus (see Fig. 42).

The main lymphatic vessels are known to be under sympathetic control (Browse 1968). When the smooth muscle wall of the thoracic duct is stimulated it produces a wave of contraction that aids lymph drainage into the subclavian vein. This produces a negative pressure along the lymphatics and further assists lymph drainage. The resulting peristaltic wave within the normal human thoracic duct was found to occur at 4 beats per minute with a maximum pressure of around 10-mmHg, building up to 50 mmHg if obstructed (Kinmonth and Sharpey-Schafer, 1959). The thoracic duct pump acts as suction for the lymphatics around the body and influences the drainage of toxins from the central nervous system. Together with the pulse rate (72 bpm) and the overall influence of ventilation (respiratory frequency is 10-18 breaths per minute in adults) (Bell, Emslie-Smith and

Paterson, 1980), a separate underlying rhythm is induced which could indeed be the aforementioned 'involuntary mechanism'.

Cerebrospinal fluid (CSF) moves intracranially at the same rate as the heart (i.e. approximately 72 beats per minute at rest) and normally moves within the ventricular system of the brain at around 600ml/min. The blood flow in the carotid bodies in the neck, just after leaving the heart is 2000 ml/g/min, whereas normal blood flow in the brain is approximately 65 ml/g/min. The flow of lymph in the thoracic duct is known to be about 1 to 2 ml/min between meals, but may increase 5 to 10 times during ingestion and absorption of a meal (Bell, Emslie-Smith and Paterson, 1980). This was why all the subjects in phase 2 of this study were instructed to eat a light meal 90 minutes before each session of scans. The above data is summarised in the diagram below.

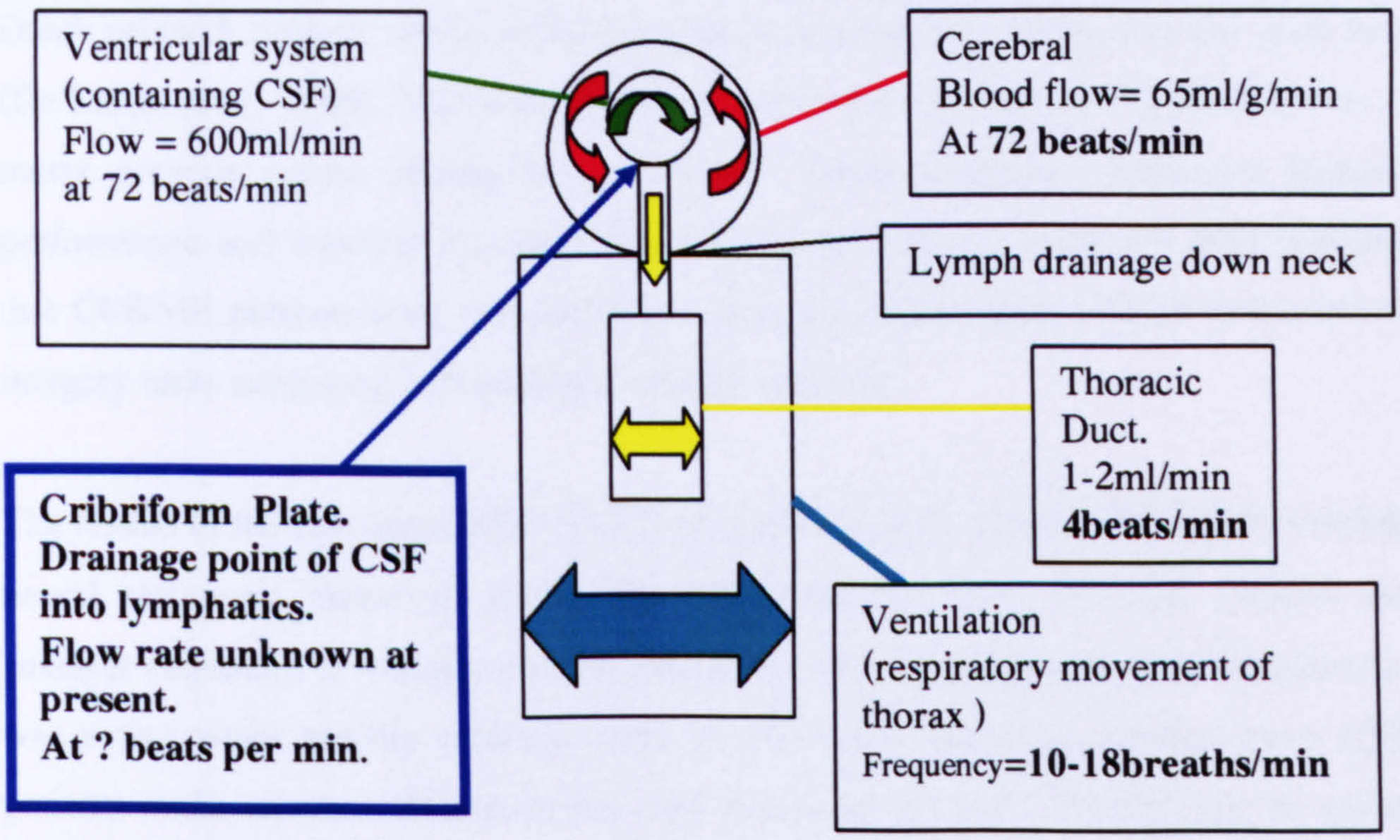



**Figure 95 Schematic diagram demonstrating the influences of fluid mechanics involved in the drainage of CSF from the neuraxis.**

Immediately arising from this present research, agreement has been reached for a future study to be undertaken at the University of Manchester's department of Fluid Mechanics and Aeronautical engineering. Researchers, using the above known parameters and

computerised models of the bio-mechanical influences affecting the lymphatic drainage of the brain are to calculate a possible range of normal values of this drainage and to investigate how this hypothesised rhythm compares with the 7-12 beats per minute of Sutherlands earliest findings (Sutherland, 1990).

## 5.4 Future challenges

### 5.4.1 Functional and pharmacological MRI studies

Functional MRI or pharmacological MR which utilises drug stimulation or suppression of certain areas of the brain and observation of resultant MR image changes can be used to determine pathophysiological dysfunction in the CNS. Future research into brain abnormalities in CFS/ME should utilise these techniques and be directed towards identifying functional disturbances in this disorder. In fact, at the present time a paper on a Dutch research project, which utilised the latter imaging techniques, has just gone to press (De Lange *et al.*, 2004). This was specifically concerned with analysing disturbances in the motor nervous system arising from CFS/ME. These researchers measured behavioural performance and cerebral activity using rapid event-related functional MRI and showed that CFS/ME patients were considerably slower on performance of both motor and visual imagery tasks compared with matched healthy controls.

The results of the functional MRI (fMRI) showed that both groups used largely overlapping neural resources. However, during the motor imagery task, CFS/ME patients evoked stronger responses in visually related structures. Also the ventral anterior cingulate cortex was active when healthy controls made an error, but remained inactive when CFS/ME patients made an error. The study has also demonstrated that CFS/ME may be associated with dysfunctional motivation and motor planning (De Lange *et al.*, 2004). This supports one of the central hypotheses of this present study that CFS/ME is a functional disorder of the brain.

### 5.4.2 Genetic research

As in all areas of medicine, genetic research has a major role to play in improving our future understanding of aetiological mechanisms that may pre-dispose patients with CFS/ME. Vladutiu and Natelson (2004) have recently discovered variant genotypes associated with muscle metabolism and physical endurance in Gulf War veterans that made them much more likely to develop CFS/ME. Clinically one can see a genetic pattern in the family history data where there is more than one family member with CFS/ME. There have been cases of occurrences of the disorder in three generations. Structural anomalies of cranial bones (Noguchi *et al.*, 2002) have been linked to genetic mutation as have spinal deformities (Chatel *et al.*, 1979). It is logical that there may be genetic predisposition in some cases that may cause anomalies in the cribriform plate and /or the spine possibly affecting drainage. It is recommended that research into this possibility is undertaken in the future.

## 5.5 Conclusion

### 5.5.1 Supporting the research hypotheses

The null hypotheses originally listed on page 45, in section 1.6.2 were:

1. There is no relationship between the mechanical dysfunction of the spine, and the incidence of the symptoms arising from CFS/ME.

2. There is no difference in the symptoms associated with CFS/ME following a chosen method of osteopathic treatment compared with those of a matched control group, who received no such treatment.

3. Any improvement of symptoms associated with CFS/ME following a chosen method of osteopathic treatment compared with those of a matched control group, who received no such treatment will not be sustainable or repeatable.

4. There is no relationship between pathological findings in the structure of the brain and the symptoms in CFS/ME.

5. There is no relationship between the symptom of muscular fatigue in CFS/ME and pathological changes in the muscle.

The clinical findings, observed by the author over the past fifteen years as presented in chapters 1 and 2, show that there is a correlation between mechanical dysfunction of the spine and the symptoms arising from CFS/ME. Even though no change in spinal movement was seen in phase 1 of the study, the observable findings in both phase 1 and 2 sufficiently support the initial research objective thus null hypothesis 1 is rejected.

The results in both phases of the study indicate that the symptoms diminished significantly following the chosen osteopathic treatment and that the improvement was sustained, thereby rejecting null hypotheses 2 and 3.

Although the changes seen in the thoracic duct scans necessitate further investigation with a larger study in future research, no abnormality has been detected in brain volume, rate of atrophy, white matter lesions, cerebral blood flow or aqueductal CSF flow in a group of patients who had satisfied rigorous diagnostic and selection criteria as a CFS/ME subject. This does not exclude the possibility that CFS/ME may result from some subtle patterns of organic brain lesions. These could produce distinctive imaging findings which might represent more severe subgroups in the CFS/ME population that have not yet been studied in this research. However, the findings clearly show that the symptom complex described as CFS/ME occurs in patients with no identifiable cerebral abnormality. Consequently null hypothesis 4 is accepted. These findings point to another cause, undetected by existing MRI techniques used in this study, of symptoms associated with CFS/ME which may be impaired lymphatic drainage.

The results of the EMG study have demonstrated that the reduction in motor units recruited in CFS/ME is significantly no different to the healthy group following exercise and does

not change with treatment (see ch. 4). This suggests that there are no changes in the ion transfer within the motor units of the muscle in CFS/ME and implies that the lactic acid distribution remains constant. This finding is supported by the aforementioned recent research which concluded that the problem is not due to reduced blood flow (McCully *et al.*, 2003).

The results implied that there is no intrinsic muscle disorder. Consequently null hypothesis 5 is accepted (see page 45). These findings point to another cause of the reduction of muscle performance associated with CFS/ME. A plausible alternative explanation of the fatigue may be a reduction of the lymphatic drainage of the muscle.

However the findings of both phases in this study have shown that the chosen osteopathic treatment does improve the muscle performance, without the use of an exercise regime. It may be that the treatment's success is due to aiding lymph drainage, but perhaps the massage techniques generate heat which may benefit the muscle performance. Or it may be that the author's treatment stimulates the motor nerve conduction. The reason for the muscular dysfunction in CFS/ME continues to remain an enigma that warrants further research in these areas.

The findings of this thesis shed further light into each of the original objectives and warrant the necessity for further investigation to the neurolymphatic pathways detailed in this work. As technological advances continue, especially in radiological procedures and neuroscience, it is only a matter of time before the unanswered questions raised by this thesis will be explained.

## APPENDIX A1: Ethical Approval

Both clinical trials in phases one and two carried out by the author and his co-workers were approved by local health authorities research ethics committees, the details of which are listed below:

Phase 1:

Approved by Bury and Rochdale Health Authority Research Ethics Committee;
Chairman: Mrs C A Hopkins, January 1995. Project No. BREC 16.

Approved by Salford and Trafford Health Authority Research Ethics Committee;
Chairman: Mrs J. Blunt, February 1995. Project No. 95020.

Phase 2:

Approved by Bury and Rochdale Health Authority Research Ethics Committee;
Chairman: Mr I Buchanan, February 2000. Project No. BRLEC 62.

## APPENDIX A2: Diagnostic criteria for CFS/ME

1. The London criteria (Tyrrell *et al.*, 1994) used by *Action for ME* in phase 1.

# THE 'LONDON' CRITERIA

### DIAGNOSTIC CRITERIA FOR THE SELECTION OF SUBJECTS FOR RESEARCH INTO ME/PVFS

These three criteria must all be present for the diagnosis of ME/PVFS to be made. If any of these are not present the volunteer research subject should not be used for the purpose of research into ME/PVFS and an alternative diagnosis should be keenly sought.

A) Exercise-induced fatigue precipitated by trivially small exertion-physical or mental-relative to the patient's previous exercise tolerance.

B) Impairment of short-term memory and loss of powers of concentration, usually coupled with other neurological and psychological disturbances such as emotional lability, nominal dysphasia, disturbed sleep patterns, disequilibrium or tinnitus.

C) Fluctuation of symptoms, usually precipitated by either physical or mental exercise (see b) above.

These symptoms should have been present for at least six months and should be ongoing.

### A VIRAL TRIGGER?

Although ME/PVFS typically follows an infection, usually a viral illness (which may be subclinical) in a previously fit and active person, it has also been observed to be triggered by other factors such as immunisations, life traumas and exposure to chemicals. Furthermore, in a minority of patients, ME/PVFS has a gradual onset with no apparent triggering factor. For these reasons proof of a preceding viral illness is not a prerequisite for diagnosis or inclusion in a study group.

### ASSESSMENT, INVESTIGATION AND DIAGNOSIS

When diagnosing ME for research purposes, particular attention must be paid to two factors:

- Many of the symptoms and signs evident in people suffering from ME/PVFS could be due to a large number of important diseases/conditions.
- ME may run parallel with other diseases having similar symptoms and signs.

Because it is vital that the ME study groups we use in research are as 'pure' as possible, the existence of a parallel disease would be grounds for disqualification. The most common alternative diagnosis/parallel diseases to be borne in mind before referring a research subject volunteer to an ME study group can be considered under the following headings:

| | |
|---|---|
| Chronic infections: | toxoplasmosis, Lyme disease, HIV infection, chronic active hepatitis, schistosmosiasis, brucellosis, occult sepsis, tuberculosis, giardia. |
| Endocrine disorders: | hypothyroidism, thyrotoxicosis, Addison's disease. Cushing's syndrome, diabetes mellitus, hyperparathyroidism. |
| Neuromuscular disorders: | Myasthenia gravis, multiple sclerosis, mitochondrial myopathy, Parkinson's disease. |
| Cardio-vascular disorders: | Cardiac ischaemia. |

Metabolic disorders: Sleep apnoea syndrome, chronic renal failure.

Malignant disease: Occult tumours such as undiagnosed lymphomas, retroperitoneal sarcomas: renal and liver tumours; frontal lobe tumours.

Auto-immune disease: Rheumatoid arthritis, systemic lupus Erythematosus, thyroiditis, Sjogrens syndrome.

Haematological disorders: Leukaemias and anaemias of varying origin.

Miscellaneous: Heavy metal poisoning, chronic intoxications due to prolonged exposure to chemicals such as petrol, benzene, organo-phosphorous compounds and methylene chloride; drug side effects such as those due to beta-blockers and long-term benzodiazepine usage; chronic alcoholism; celiac disease.

Psychiatric: Primary depressive illness, anxiety neurosis.

## OTHER REASONS FOR EXCLUSION FROM RESEARCH INTO ME

Of particular importance is to eliminate chronic fatigue primarily associated with psychological factors. If there are signs of persistent anhedonia, apathy, low self-esteem, feelings of worthlessness and guilt, the possibility of primary depressive illness should be actively considered and, if there is any doubt whatsoever, the subject eliminated from the research study.

If the subject has had any other diseases or conditions in the last three months they should be excluded from research into ME.

If the subject has taken any treatments – orthodox, complementary or nutritional- in the last three months they may have to be excluded from certain research projects.

## OTHER SYMPTOMS SOMETIMES EXPERIENCED BY PEOPLE WITH ME/PVFS

Many symptoms are experienced by people suffering from ME/PVFS and in the right symptomatic context they contribute to the validity of the diagnosis. Nevertheless, not all people suffering from ME/PVFS experience all these symptoms and their absence does not exclude the condition.

These can be subdivided into the following two categories:

Autonomic Bouts of inappropriate night or day-time sweating: reynauds phenomenon; postural hypotension; disturbance of bowel motility manifesting as a recurrent diarrhoea or occasionally constipation (these symptoms are frequently indistinguishable from those of IBS); photophobia; blurred vision due to disturbed accommodation; hyperacusis; increased frequency of micturition; nocturia.

Immunological Symptoms suggesting persistent viral infection, e.g. episodes of low grade fever (i.e. not exceeding an oral temperature of 38.6C) combined with feeling feverish (i.e. a down-regulated 'thermostat'); sore throat which may be persistent or recurrent (i.e. present for at least one week per month); arthralgia of a fixed or migratory nature.

This list is by no means exhaustive; headaches, nausea and bloating, for instance are common symptoms but are not sufficiently discriminative because of their widespread occurrence in many other disorders. The curious intolerance to alcohol and hypersensitivity to drugs are highly specific in this context. It should also be emphasised that the symptoms of ME tend to vary capriciously from hour to hour and day by day. Nevertheless it is absolutely characteristic that they tend to be exacerbated by physical or mental exertion and this association should always be sought whilst taking the history.

2. The CDC criteria (Fukuda *et al.*, 1994) are the more accepted criteria and were thus used by the author in both clinical trials.

**The Centre for Disease Control revised criteria for Chronic Fatigue Syndrome**

**(Adapted from Fig. 2, Fukuda, *et al.*, 1994).**

I Clinically evaluate cases of chronic fatigue by:

A. History and physical examination.
B. Mental status examination (abnormalities require psychiatric, Psychological, or neurological examination)
C. Tests (abnormal results that strongly suggest an exclusionary condition must be resolved)
   1. Screening Lab Tests: full blood count, erythrocyte sedimentation rate, alanine aminotransferase, total protein, albumin, globulin, alkaline phosphatase, calcium, phosphate, glucose, urea and electrolytes, creatinine, thyroid stimulating hormone and urinalysis.
   2. Additional tests as clinically indicated to exclude other diagnoses.

*EXCLUDE IF ANOTHER CAUSE FOR CHRONIC FATIGUE IS FOUND*

II Classify as either chronic fatigue syndrome or idiopathic chronic fatigue if fatigue persists or relapses for 6 months or more.

*CLASSIFY AS IDIOPATHIC CHRONIC FATIGUE IF FATIGUE SEVERITY OR SYMPTOM CRITERIA FOR CHRONIC FATIGUE ARE NOT MET.*

Classify as chronic fatigue if both of the following criteria are met:

A) Unexplained persistent or relapsing fatigue of new or definite onset that is not due to ongoing exertion, is not relieved by rest and results in substantial reduction in previous levels of activity.

B) Four or more of the following symptoms are concurrently present for 6 months or longer.

1. Impaired memory or concentration (severe enough to reduce levels of occupational, social and personal activity.)
2. Sore throat.
3. Tender cervical or axillary lymph nodes.
4. Muscle pain
5. Multijoint pain (without joint swelling or redness).
6. New headaches
7. Unrefreshing sleep
8. Post-exertion malaise (lasting, more than 24 hours)

## APPENDIX A3: Psychiatric/psychological tests

Both the HADS and the SCAN systems below were used by the consultant psychiatrist to exclude unsuitable volunteers from the second clinical trial.

# 1. The Hospital Anxiety and Depression Scale (Zigmond and Snaith, 1983)

Name..... Date.....

**Clinicians are aware that emotions play an important part in most illnesses. If your clinician knows about these feelings she or he will be able to help you more.**
**This questionnaire is designed to help your clinician to know how you feel. Ignore the numbers printed on the left of the questionnaire. Read each item and underline the response which comes closest to how you have felt in the past week. Don't take too long over your replies. Your immediate reaction will probably be more accurate than a long thought-out response.**

| | | |
|---|---|---|
| | A | **I feel tense or 'wound up':** |
| | 3 | Most of the time |
| | 2 | A lot of the time |
| | 1 | From time to time, occasionally |
| | 0 | Not at all |
| | | |
| | D | **I still enjoy the things I used to enjoy:** |
| | 0 | Definitely as much |
| | 1 | Not quite so much |
| | 2 | Only a little |
| | 3 | Hardly at all |
| | | |
| . | A | **I get a sort of frightened feeling as if something awful is about to happen:** |
| | 3 | Very definitely and quite badly |
| | 2 | Yes, but not too badly |
| | 1 | A little, but it doesn't worry me |
| | 0 | Not at all |
| | | |
| | D | **I can laugh and see the funny side of things:** |
| | 0 | As much as I always could |
| | 1 | Not quite so much now |
| | 2 | Definitely not quite so much now |
| | 3 | Not at all |

| | | |
|---|---|---|
| | A | **Worrying thoughts go through my mind:** |
| | 3 | A great deal of the time |
| | 2 | A lot of the time |
| | 1 | From time to time but not too often |
| | 0 | Not at all |

| | | |
|---|---|---|
| D | | **I feel cheerful:** |
| 3 | | Not at all |
| 2 | | Not often |
| 1 | | Sometimes |
| 0 | | Most of the time |

| | | |
|---|---|---|
| | A | **I can sit at ease and feel relaxed:** |
| | 0 | Definitely |
| | 1 | Usually |
| | 2 | Not often |
| | 3 | Not at all |

| | | |
|---|---|---|
| D | | **I feel as if I am slowed down:** |
| 3 | | Nearly all the time |
| 2 | | Very often |
| 1 | | Sometimes |
| 0 | | Not at all |

| | | |
|---|---|---|
| | A | **I get a sort of frightened feeling like 'butterflies' in the stomach:** |
| | 0 | Not at all |
| | 1 | Occasionally |
| | 2 | Quite often |
| | 3 | Very often |

| | | |
|---|---|---|
| D | | **I have lost interest in my appearance:** |
| 3 | | Definitely |
| 2 | | I don't take as much care as I should |
| 1 | | I may not take quite as much care |
| 0 | | I take just as much care as ever |

| | | |
|---|---|---|
| | A | **I feel restless as if I have to be on the move:** |
| | 3 | Very much indeed |
| | 2 | Quite a lot |
| | 1 | Not very much |
| | 0 | Not at all |

| | | |
|---|---|---|
| D | | **I look forward with enjoyment to things:** |
| 0 | | As much as I ever did |
| 1 | | Rather less than I used to |
| 2 | | Definitely less than I used to |
| 3 | | Hardly at all |
| | A | **I get sudden feelings of panic:** |
| | 3 | Very often indeed |
| | 2 | Quite often |
| | 1 | Not very often |
| | 0 | Not at all |
| D | | **I can enjoy a good book or radio or TV programme** |
| 0 | | Often |
| 1 | | Sometimes |
| 2 | | Not often |
| 3 | | Very seldom |

Now check that you have answered all the questions.

For office use only:

D: Borderline 8-10
A: Borderline 8-10

## 2. The SCAN system (Schedules for Clinical Assessment in Neuropsychiatry) (Mavreas, 1990; Tomov and Nikolov, 1990; Ustan, 1990; Wing, 1990)

### DEVELOPMENT AND BASIC PRINCIPLES

The SCAN system is a set of instruments and manuals aimed at assessing, measuring and classifying the psychopathology and behavior associated with the major psychiatric disorders of adult life. The SCAN text has 3 components: the tenth edition of the Present State Examination (PSE10), the Item Group Checklist (IGC) and the Clinical History Schedule (CHS).

PSE10 itself has two parts. Part I covers somatoform, dissociative, anxiety, depressive and bipolar disorders, and problems associated with eating, alcohol and other substance abuse. There is also a screen for Part II conditions. Part II covers psychotic and cognitive disorders and observed abnormalities of speech, affect and behavior.

The SCAN system contains two other essential elements: the Glossary of differential definitions and CATEGO, a set of computer programs for processing SCAN data and providing output.

Data from the schedules can be entered into CATEGO in a variety of ways: on the SCAN Schedules themselves, on SCAN Coding Sheets, and into a computer program. Output from CATEGO is presented as a series of options, including a range of profiles of symptom and IGC scores, an Index of Definition, ICD-10 and DSM categories, a prediagnostic profile of categories, and a list of items rated present.

In its complete form, used in this study the SCAN text is intended for use only by clinicians with an adequate knowledge of psychopathology who have taken a course at a WHO-designated SCAN training center.

SCAN represents the latest stage in a 30-year line of development that began in the late 1950s. PSE9 was the first of the series to be published, following 15 years of work on

earlier versions, including two large multicenter international projects - the US-UK Diagnostic Project (1972) and the International Pilot Study of Schizophrenia (IPSS; WHO, 1973). PSE9 consists of only 140 items, compared to the 500-600 of PSE7 and PSE8. It has been widely used, as evidenced by its translation into 35 or more languages, but many users have regretted that the longer preceding editions were withdrawn; they would have preferred a choice, which is now provided by PSE10.

The principles underlying the PSE have changed very little during these developments but they have gradually been applied to a broader range of disorders, have come to incorporate more and more aspects of the clinical history and, through the use of an increasingly complex technology, have been preserved without loss of the basic clinical bottom-up approach and user friendliness. An understanding of the history is therefore a useful basis for an appreciation of SCAN.

The central principle of the PSE is that the interview, although substantially structured, retains the features of a clinical examination. The aim of the interviewer is to discover which of a comprehensive list of phenomena have been present during a designated period of time and with what degree of severity. The items listed are differentially defined in this Glossary, with which the interviewer is expected to be closely familiar. The examination is therefore based on a process of matching the respondent's behavior and description of subjective experiences against the clinical definitions provided. Applying the central principle means that a rich data base of differentially-defined clinical phenomena forms the core of SCAN. Numerous classifying algorithms can be applied to generate 'diagnoses' according to the criteria of schools that provide sufficiently operational rules. Two of these (ICD, and DSM since its third revision) have won wide international acceptance. But any other set of rules can be applied. "The flexibility of this approach, the incorporation of detailed cross-examination, which allows changes in the order and wording of questions according to the way the interview is going, the freedom of the clinician to pursue some lines of enquiry while cutting off others, the fact that the examiner and not the patient makes the judgement as to whether a symptom is present, do not seriously impair the reliability of the procedure" (Wing *et al.*, 1967).

This statement was based on experience with the third to the fifth editions of the PSE and it still holds good with PSE10. Preparations for a tenth edition of the PSE were started in 1980, in anticipation of the tenth edition of the ICD. The major emphasis of correspondents was on broadening the content, both by returning to the larger item-pool of PSE7 and PSE8, and by adding new sections to cover somatoform, dissociative and eating disorders, alcohol and drug misuse, and cognitive impairments. A second suggestion was that an extra rating point was needed to extend the 0-1-2 scales of severity used for most PSE9 items, allowing a mild or 'sub-clinical' level to be used, particularly in population surveys. A third, very obvious, requirement was for a better system for rating episodes of disorder, adding other information relevant to the history and to the causes of disorder, and processing all the information by means of one set of computer programs.

## THE PURPOSE OF THE SCAN SYSTEM

The purpose of the SCAN system is to provide comprehensive, accurate and technically specifiable means of describing and classifying psychiatric phenomena, in order to make comparisons.

Training in SCAN techniques provides a common clinical language in which to compare and contrast the experiences and behavior of patients, to consider the usage of different clinical schools in relation to a common reference system, to compare epidemiological and public health data more precisely, and to make the results of scientific research readily available for replication between centres.

## CLINICAL CROSS-EXAMINATION

The function of the Glossary is to support the process of clinical cross-examination, which is the central method of obtaining information about the respondent's subjective experiences. Training in the differential definitions provides the examiner with a set of

'item concepts', which are matched against the respondent's descriptions. Only when the description matches the concept does the examiner make the rating. This process helps to eliminate syndromal, diagnostic and other biased misunderstandings.

Considerable training and experience is needed before the probe system in the SCAN text can be used flexibly enough in close conjunction with the Glossary to ensure that the ratings most accurately fit the phenomena.

## APPENDIX A4: Information and consent forms

During the course of the clinical trials outlined in this thesis all experimentation on human volunteers was subject to intense scrutiny by the relevant health authority research ethics committee as noted in Appendix A1. A standard requirement of all ethically approved research is to inform patients, and their general practitioners, of all procedures to be undertaken and any relevant consequences of their involvement in the study. Examples of the many information and consent sheets used are included in this section.

**The involvement of cerebrospinal fluid and lymphatic drainage in chronic fatigue syndrome: a pilot study.**

**CONTROL GROUP URGENTLY NEEDED FOR THE ABOVE RESEARCH PROJECT**

**IF YOU ARE FIT AND HEALTHY AND WISH TO HELP AN IMPORTANT NEW RESEARCH PROJECT PLEASE READ THE FOLLOWING**

A new research project is about to begin at the University of Salford, Greater Manchester. This projects hopes to spread light on the processes involved in the body that lead to Chronic Fatigue Syndrome (commonly known as M.E.) and how they are affected by a treatment program developed by osteopath Raymond Perrin. WE URGENTLY NEED TEN HEALTHY VOLUNTEERS WHO WISH TO HELP US DEMONSTRATE A POSSIBLE PHYSICAL NATURE OF THE DISEASE.

The overall aims of this project are:

1. To examine any changes in the brain and the involvement of alterations in fluid that flows around the brain and the spine. (This is known as the cerebrospinal fluid).

2. To analyse changes in the flow and volume of the lymphatic fluid in the neck and chest.

One of the possible roles of cerebrospinal fluid is to drain poisons/toxins from the brain and spine to the lymph vessels in the head and back. The lymphatic fluid flows into the neck and chest area and eventually into the blood stream just below the collar bones. By recording a visible increase in volume of fluid in the lymph vessels and an increase of cerebrospinal fluid volume in M.E./Chronic Fatigue Syndrome patients with a noticeable

reduction in fluid movement we will demonstrate a possible congestion of drainage in this region.

3. To study the effects of osteopathic treatment on the cerebrospinal fluid and the lymphatic drainage by non-invasive techniques before and following a year long course of treatment.

YOU WILL BE REQUIRED TO HAVE THE FOLLOWING TESTS:

Scanning of the head neck and chest at two separate occasions. The brain and lymph vessels of the neck and chest will be studied by Magnetic Resonance Imaging. This form of scanning involves no radiation and thus can be repeated without any harm. These studies will be undertaken at the Department of Diagnostic Radiology, University of Manchester.

.

2) Muscle fatigue and physical function will be measured by a Kincom isokinetic machine and surface electromyography. The former is a specially constructed chair in which you will be asked to press your leg against a pad that is connected to a computer. This will then measure the amount of fatigue in your thigh muscle. The surface electromyography uses rubber pads that are placed on the skin. Electromyography measures the activity of the muscle and causes no pain.

You are not eligible if you suffer from a primary depressive illness, or have suffered from any other psychological or neurological disorder, including claustrophobia. **(N.B. A consultation with a consultant psychiatrist has been arranged before you are accepted on the project.)** Any bodily-metallic object will disqualify yourself from being scanned.

Simple questionnaires will have to be completed at the beginning of the project and at the end of the twelve months.

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There are no known potential hazards in this study. The Magnetic Resonance Imaging scan may appear daunting, although it presents no hazard. The procedure requires you to lie quite still in a tunnel which may seem claustrophobic and surprisingly noisy. However expert personnel will be present to explain the points to you. There is a possibility that the imaging may reveal another disease state. Any abnormality discovered whilst scanning research subjects will be immediately brought to the attention of your GP. In fact your doctor will be informed of any results of the research (even ones showing no abnormalities). It is important to realise that this information on your medical records may have a bearing on future health insurance/mortgage provision.

Lastly, some filming will take place to record the research (your face will not be filmed preserving anonymity).

ALL EXPENSES WILL BE REIMBURSED IN FULL.

If you wish to volunteer or if you have any further queries please contact me at the address below as soon as possible.

Yours Faithfully,

Raymond N. Perrin D.O.

## INFORMATION FOR SUBJECTS INVOLVED IN THE ABOVE RESEARCH PROJECT

Thank you for volunteering to be a research subject. You are one of 10 patients who have been selected to help our research. Before you sign the consent form and we begin the actual project there are obviously some important points to clarify. This information sheet is to allow you to understand the reasons for the research, what we are going to do over the next year, and what we hope to achieve.

The osteopathic treatment of Chronic fatigue syndrome (commonly known as M.E.) developed by myself consists of gentle manipulation of the spine and massage to stimulate drainage in lymphatic vessels of the head, neck, back and chest. In a previous research project this approach produced an improvement of the condition (Perrin *et al.*,1998, J. Medical Engineering and Technology, 22, 1-13) compared with a group of patients treated in other programmes by different conventional therapies (i.e. Psychotherapy, exercise and diet programmes and antidepressants). The question is how and why the treatment works? This projects hopes to spread light on the processes involved in the body that lead to M.E./Chronic fatigue syndrome and how they are affected by my treatment program.

The overall aims of this project are:
1. To examine any changes in the brain and the involvement of alterations in fluid that flows around the brain and the spine. (This is known as the cerebrospinal fluid).
2. To analyse changes in the flow and volume of the lymphatic fluid in the neck and chest. One of the possible roles of cerebrospinal fluid is to drain poisons/toxins from the brain and spine to the lymph vessels in the head and back. The lymphatic fluid flows into the neck and chest area and eventually into the blood stream just below the collar bones. By recording a visible increase in volume of fluid in the vessels and an increase of Cerebrospinal fluid volume in M.E./Chronic fatigue syndrome patients with a noticeable reduction in fluid movement we will demonstrate a possible congestion of drainage in this region.
3. To study the effects of osteopathic treatment on the cerebrospinal fluid and the lymphatic drainage by non-invasive techniques before and following a year long course of treatment.

You must have been previously tested for any other possible cause of the symptoms. Also, if you suffer from a primary depressive illness, or have suffered from any other psychological or neurological disorder, including claustrophobia, then you must inform us immediately before commencement of the study. **(N.B. A consultation with a consultant psychiatrist has been arranged before you are accepted on the project.)** Any bodily-metallic object will disqualify yourself from being scanned. You must not begin any other new treatment for M.E. /CFS for the duration of the project and you must not have received any physical therapy for your present symptoms during the previous six months.

The method of investigation will involve the following:
**1.** The brain and lymph vessels of the neck and chest will be studied by Magnetic Resonance Imaging. This form of scanning involves no radiation and thus can be repeated

without any harm. These studies will be undertaken at the Department of Diagnostic Radiology, University of Manchester.
2. Level of fatigue and of physical function will be measured by a Kincom isokinetic machine and surface electromyography. The former is a specially constructed chair in which you will be asked to press your leg against a pad that is connected to a computer. This will then measure the amount of fatigue in your thigh muscle. The surface electromyography uses rubber pads that are placed on the skin. Electromyography measures the activity of the muscle and causes no pain.

You will receive weekly sessions of osteopathic treatment from myself based on the protocol devised over the past ten years working in a practice specializing in the management of ME/Chronic fatigue syndrome patients. The sessions will include
i) Articulation and gentle manipulation of the spine and the ribcage.
ii) Manual stretching and massage of the muscles in the neck and trunk.
iii) Manual lymphatic drainage using effleurage (stroking techniques) on the head, neck, back and chest.
iv) Cranio-sacral therapy (applying gentle pressure to the head and low back) to stimulate the movement of the cerebrospinal fluid.

Questionnaires will have to be completed at the beginning and end of the project. You will also have to follow a self-massage program to further encourage lymphatic drainage from the brain and spine. You will also be instructed in gentle mobility exercises and advised to use regular contrast bathing techniques (hot & cold compresses) to reduce inflammation of the spine.

You are expected to keep the same weight throughout the year long project. Any major change in weight will disqualify you from the research project.

There are no known potential hazards in this study. The scan may appear daunting, although it presents no hazard. The procedure requires you to lie quite still in a tunnel which may seem claustrophobic and surprisingly noisy. However expert personnel will be present to explain the points to you. There is one problem that may arise when we scan your body. Magnetic resonance imaging may reveal another disease state. Any abnormality discovered whilst scanning research subjects will be immediately brought to the attention of your GP. In fact your doctor will be informed of any results of the research (even ones showing no abnormalities). It is important to realise that this information on your medical records may have a bearing on future health insurance/ mortgage provision.

The treatment itself may aggravate symptoms in the initial stages but it is very rare to have lasting harmful or painful consequence. Lastly, some filming will take place to record the research (your face will not be filmed preserving anonymity).

Thank you again for your participation. If you have any further queries please contact me at my practice.
Yours Faithfully,

Raymond N. Perrin D.O.

## ME/CFS- CONTROL GROUP A. CONSENT FORM
## (me/cfs sufferers)

Dear .....,

Thank you for volunteering to be a control group member in the research into the treatment of M.E./Chronic Fatigue Syndrome by osteopathic methods.

By volunteering for this project you agree to the following:

1. To undergo Magnetic Resonance Scanning of the head neck and chest four times in total over a period of one year. (Twice at the beginning of the trial and twice at the end of the year long treatment).
2. To allow the testing of post-exercise muscle fatigue before and after a year long period using the 'Kincom' isokinetic machine and to have your muscles tested by surface electromyogram (sEMG).
3. To attend a preliminary interview with a consultant psychiatrist to evaluate your mental and emotional state.
4. To avoid any osteopathic or other manual treatment for the treatment of ME/CFS for the duration of the trial.
5. To supply reliable information to the researchers concerning any other therapy for that you may undergo for ME/CFS during the year's trial.
6. To complete two sets of questionnaires relating to your health at the beginning and end of the project.
7. To allow the filming of consultations, examinations and tests by Mr Perrin, as long as anonymity is preserved at all times.

N.B. You have the right to leave the project at any time.

Please print your name clearly below, sign, witness and date the form below:

.....

I ..... Agree to the seven terms mentioned above and wish to join the research project as one of the ME/CFS sufferers control group for a period of one year.

Signed: .....Date: : : 2000

Witnessed by .....Date: : : 2000

## LETTER SEEKING GENERAL PRACTITIONER'S CONSENT RE: MEMBER OF PATIENT GROUP

To Dr. .....

RE: .....

D.O.B. .....

ADDRESS .....
.....

Dear Dr. .....,
This patient has volunteered to take part in a research program involving specialist osteopathic treatment for the fatigue condition diagnosed as myalgic encephalomyelitis/ chronic fatigue syndrome.

I have been involved since 1989 in the treatment of patients with symptoms associated with M.E./CFS and have spent the past eleven years researching into this debilitating disorder. I have published two scientific papers (1, 2) and written information booklets and treatment guides for this disease. I completed a controlled trial into the efficiency of osteopathic treatment for symptoms associated with M.E. This was carried out over a two year period at Salford university and Hope hospital. The research carried out together with bio-engineer Prof. Jack Edwards and health psychologist Dr. Pat Hartley demonstrated that my treatment techniques developed since 1989 did help reduce the symptoms and restored patients to a much better quality of life(2).

I am now involved in further research at Salford University's dept. of biological sciences for a doctorate in the treatment of M.E./CFS, together with neuro-biologist Dr. Vic Pentreath. The research findings at present point to alterations in the flow of cerebrospinal fluid and lymphatic drainage of the neuraxis. My treatment aims at improving the drainage from the head, and spine using standard osteopathic techniques.

During the year-long clinical trials we intend to use M.R. scanning of the brain, cervical and thoracic lymphatics, and to test muscle fatigue utilising the Kin-Com isokinetics machine with surface EMG. These investigative techniques will all be performed by highly qualified specialists at the Universities of Salford and Manchester. Your patient has been explained the procedures involved and has agreed to take part, subject to your approval. Please find attached a copy of the CDC criteria for CFS.

If you feel that the patient does not fulfil the strict criteria please inform us. Also if you feel that the patient will not be suitable for the research for any other reason please let us know as soon as possible. If you do feel that the patient would be a suitable candidate for the project, please fill out the enclosed consent form and return it to us in the stamped addressed envelope.

This research project is extremely important and is a very costly undertaking. Due to the controversy surrounding the acceptance of this disorder it is imperative that we are as thorough as possible in using only patients that fulfil the criteria. To this end we have enlisted the services of a consultant psychiatrist to conduct a preliminary interview for a detailed psychological profile of the patient. You as the patient's general practitioner/consultant are needed to give an independent clarification of the diagnosis before the patient is accepted onto our subject group.

We are aware of the limited time you have in your day, but we ask you to give the matter of consent serious thought before replying. As with the first stage of this project, ethical approval has been given from Bury & Rochdale Health Authority research ethics committee. If you have any further questions please do not hesitate in contacting myself on 0161 773 0123.

Thank you for your co-operation,

Yours Sincerely,

Raymond N. Perrin D.O.
Dept. of Biological Sciences
University of Salford.

REFERENCES:

1. PERRIN R, N. 1993 CHRONIC FATIGUE SYNDROME, A REVIEW FROM THE BIOMECHANICAL PERSPECTIVE. *BRITISH OSTEOPATHIC JOURNAL*; VOL XI.

2. PERRIN RN, EDWARDS J AND HARTLEY P (JANUARY/FEBRUARY 1998) AN EVALUATION OF THE EFFECTIVENESS OF OSTEOPATHIC TREATMENT ON SYMPTOMS ASSOCIATED WITH MYALGIC ENCEPHALOMYELITIS. A PRELIMINARY REPORT. *JOURNAL OF MEDICAL ENGINEERING AND TECHNOLOGY*, 22(1), 1-13.

Tel: 0161 773 0123 Fax: 0161 773 7288 Email forme@eng.net

**GPCFS1**

# GENERAL PRACTITIONERS AUTHORISATION FORM

## ME/CFS RESEARCH PROJECT - UNIVERSITY OF SALFORD

RE: Patient's name.....

Address.....

D.O.B.....

I, Dr. .....agree that the above named patient may be chosen as a subject in the patient group for the research project into the involvement of cerebrospinal fluid and lymphatic drainage in chronic fatigue syndrome (CFS).

I verify that he/she fulfils the CDC criteria for chronic fatigue syndrome as defined by Fekuda *et al* (1994).

Signed: .....

Date: .....:.....:.....

## LETTER SEEKING GENERAL PRACTITIONER'S CONSENT RE: MEMBER OF HEALTHY CONTROL GROUP

To Dr. .....

RE: .....

D.O.B. .....

ADDRESS .....
.....

Dear Dr. .....+,
This patient has volunteered to be a member of a healthy-norm control group in a research program involving specialist osteopathic treatment for the fatigue condition diagnosed as myalgic encephalomyelitis/ chronic fatigue syndrome.

I have been involved since 1989 in the treatment of patients with symptoms associated with CFS/ME and have spent the past eleven years researching into this debilitating disorder. I have published two scientific papers (1,2) and written information booklets and treatment guides for this disease. I completed a controlled trial into the efficiency of osteopathic treatment for symptoms associated with CFS/ME This was carried out over a two year period at Salford university and Hope hospital. The research carried out together with bio-engineer Prof. Jack Edwards and health psychologist Dr. Pat Hartley demonstrated that my treatment techniques developed since 1989 did help reduce the symptoms and restored patients to a much better quality of life(2).

I am now involved in further research at Salford University's dept. of biological sciences for a doctorate in the treatment of CFS/ME, together with neuro-biologist Dr. Vic Pentreath. The research findings at present point to alterations in the flow of cerebrospinal fluid and lymphatic drainage of the neuraxis. My treatment aims at improving the drainage from the head, and spine using standard osteopathic techniques.

During the year-long clinical trials we intend to use M.R. scanning of the brain, cervical and thoracic lymphatics, and to test muscle fatigue utilising the Kin-Com isokinetics machine with surface EMG. These investigative techniques will all be performed by highly qualified specialists at the Universities of Salford and Manchester. Your patient has been explained the procedures involved and has agreed to take part, subject to your approval.

**NO TREATMENT WILL BE GIVEN BY THE RESEARCH TEAM: THE PATIENT HAS BEEN GIVEN PERMISSION TO RECEIVE ANY TREATMENT OF THEIR CHOOSING WITH THE EXCEPTION OF OSTEOPATHY, PHYSIOTHERAPY AND MASSAGE (Without prior permission from the research team) FOR THE DURATION OF THE YEAR-LONG PROJECT.**

If you feel that the patient will not be suitable for the research for any reason please let us know as soon as possible. If you do feel that the patient would be a suitable candidate for the project, please fill out the enclosed consent form and return it to us in the stamped addressed envelope.

We are aware of the limited time you have in your day, but we ask you to give the matter of consent serious thought before replying. As with the first stage of this project, ethical approval has been given from Bury & Rochdale Health Authority research ethics committee. If you have any further questions please do not hesitate in contacting myself on 0161 773 0123.

Thank you for your co-operation,

Yours Sincerely,

Raymond N. Perrin D.O.
Dept. of Biological Sciences
University of Salford.

REFERENCES:

3. PERRIN RN. 1993 CHRONIC FATIGUE SYNDROME, A REVIEW FROM THE BIOMECHANICAL PERSPECTIVE. *BRITISH OSTEOPATHIC JOURNAL*; VOL XI.

4. PERRIN RN, EDWARDS J AND HARTLEY P (JANUARY/FEBRUARY 1998) AN EVALUATION OF THE EFFECTIVENESS OF OSTEOPATHIC TREATMENT ON SYMPTOMS ASSOCIATED WITH MYALGIC ENCEPHALOMYELITIS. A PRELIMINARY REPORT. *JOURNAL OF MEDICAL ENGINEERING AND TECHNOLOGY*, 22(1), 1-13.

Tel: 0161 773 0123 Fax: 0161 773 7288 Email forme@eng.net

**GPCFS3**

# GENERAL PRACTITIONERS AUTHORISATION FORM

## CFS/ME RESEARCH PROJECT - UNIVERSITY OF SALFORD

RE: Patient's name.....

Address.....

D.O.B.....

I, Dr. .....agree that the above named patient may be chosen as a member of the control group for the research project into the involvement of cerebrospinal fluid and lymphatic drainage in chronic fatigue syndrome (CFS).

I verify that he/she is in good health and that there are no medical reasons why he/she cannot be part of this study.

Signed: .....

Date: .....:.....:.....

## APPENDIX A5: Examples of research subjects' records

Code: RVO5

Sex: Male

Age: 52

Occupation: Part time social worker (18hrs per week)

Pastimes/hobbies (before ill) Amateur dramatics

Status: Married; 2 sons aged 25 and 29

Date of Initial Consultation: 11:02:99

Height: 6' 2"

Weight: 15st. 7lb

PAST MEDICAL HISTORY:

Birth: Cord wrapped around head but no abnormalities detected after birth.

Pre-teen: Emotional Trauma: Mother left home when pt. 2 y.o.a. Stayed in children's home for two years then went to live with father.

Chronic tonsilitis, prescribed plenty of antibiotics in early years.

Suffered from boils for no apparent reason.

Chicken pox

Teenage Yrs: 16+ fell off motorbike several times injuring head.

Adulthood 18yrs+: Tonsilectomy 19yoa.

Emotional Trauma: Father died when pt was only 24 y.o.a.

1 Brother and 2 sisters all seriously ill

Knocked off bike 1987; Injured head and neck.

Oesophagitis: 1988 treated with zantac and losec

Glandular Fever: 1989

Emotional Stress: Marital and work related mental stress.

Onset of symptoms related to CFS/ME: 1989/1990 insidious onset.

Blood Tests: FBC Normal; Melatonin level low, DHEA level low.

Other investigations: EEG Normal

EMG Normal

Prior Treatment: Prozac for 3 months no relief; Melatonin and DHEA for 6 months; Evening primrose oil and multivitamins taken for 2 years.

PRESENTING SYMPTOMS: Fatigue

Head Pain

'Muzziness' in head

Sleep disturbance

Vivid/weird dreams

Back pain

Neck pain

Peripheral joint pain

Myalgia

Numbness

Paraesthesia

Redness in chest

Cognitive ability reduced

Emotional state disturbed

Photophobia

Hyperacusis

Temperature regulation.

GI disturbance:IBS

GU: Irritation to bladder

Breathless

Oral Temperature (Norm 36.9): 36.3

Physical Signs of CFS/ME (see Ch. 5)

Thoracic Spine: slight tender T4/5; Flattened upper thoracic; Kyphotic lower thoracic and upper lumbar spine; Harrison sulcus in sternum.

Breast tissue: Varicose Lymph palpated in both breasts; Perrin's point +ve

Coeliac plexus region: Tender

Cranial Flow (Involuntary mechanism): Lower than normal.

Treatment Commenced: 16:06:00

36 treatment sessions in first year: Symptoms improved.

Epilogue: 13:07:04 Pt. continues to come for monthly treatment. Working longer hours with much less symptoms with occasional periods of exacerbated symptoms following too much activity or physical and mental stress.

Code: RVO6

Sex: Female

Age: 19 (20 at start of research programme)

Occupation: Unemployed (ex-student)

Pastimes/hobbies (before ill): Roller skating (dance), tapestry

Status: Single, lives with parents.

Date of Initial Consultation: 07:02:00

Height: 5' 10"

Weight: 13st

PAST MEDICAL HISTORY:

Birth: Intra-uterine scans revealed slow cranial growth. High cavity forceps.

Pre-teen: Eczema; Chronic tonsilitis, prescribed plenty of antibiotics in early years.
Genu Valgum with "irritable hip"

Teenage Yrs: Osgood Schlatters Disease.
Emotional Trauma: 14yoa father made redundant
16yoa: severe bout of gastroenteritis and tonsilitis plus mental stress of GCSE examinations at time of onset.
Emotional Trauma: 3grandparents die within a few years of each other.

Adulthood 18yrs+: Back Pain

Onset of symptoms related to CFS/ME: March 1997 sudden onset following viral infection.
Blood Tests: FBC Normal; EBV -ve

Other investigations: None

Prior Treatment: Prozac for 6 weeks taken 2 years ago, no relief.
Homeopathic medicine also taken without improvement.

PRESENTING SYMPTOMS: Fatigue
Head Pain
'Muzziness' in head
Vivid/weird dreams
Sleeps too much
Back and neck pain
Peripheral joint pain
Myalgia
Numbness and paraesthesia in extremities
Cognitive ability reduced
Anxiety
Photophobia
Temperature regulation dampened.
Pain in chest.
Taking contraceptive pill to regulate periods.

Oral Temperature (Norm 36.9): 36.6C

Physical Signs of CFS/ME (see Ch. 5)

Thoracic Spine: Flattened, slightly scoliotic mid-thoracic spine with pelvic torsion.

Breast tissue: Varicose Lymph palpated in both breasts; Perrin's point +ve

Coeliac plexus region: painful

Cranial Flow (Involuntary mechanism): Lower than normal.

Code: CP09

Sex: Female

Age: 21

Occupation: Student, degree in sports rehabilitation.

Pastimes/hobbies(before ill) modern/ballet dancing.

Status: Single

Date of Initial Consultation: 09:01:01

Height: 5' 6"

Weight: 10st. 6lb

PAST MEDICAL HISTORY:

Birth: Cord wrapped around neck but no abnormalities detected after birth.

Pre-teen: Talipes equino varus, required physiotherapy from 3 to 4yoa.

Teenage Yrs: 13yoa injured low back (L5) in a trampolening accident. Suffered low back pain and sciatica. Treated by physio.
15yoa Slipped badly on ice, fractured right radius and bruised coccyx
16yoa Coin thrown injuring bridge of nose, began to pass out the following day.

Adulthood 18yrs+:Tonsilitis 18yoa.
Emotional Trauma: Failed first year exams which increased the stress exacerbating the symptoms.
Twisted knee causing a right medial meniscus tear.

Onset of symptoms related to CFS/ME: September 1998 a year following major viral (flu) infection which never really recovered.

Blood Tests: FBC Normal; EBV -ve
Other investigations: none

Prior Treatment: Effexor (antidepressant) 75mg/day for last two years, not helped overall symptoms; Acupuncture; Reiki.

PRESENTING SYMPTOMS: Fatigue
Head Pain
'Muzziness' in head
Difficulty getting to sleep
Vivid/weird dreams
Back pain
Neck pain
Peripheral joint pain
Myalgia
Numbness in extremities
Paraesthesia in extremities
Redness in face, neck and chest.
Cognitive ability reduced
Emotional state disturbed: depressed secondary to illness.
Photophobia
Hyperacusis
Temperature regulation disturbed.
GI disturbance: IBS
GU: Irritation to bladder increased frequency
Slightly asthmatic.
Dry skin with occasional acne.
Non-exudative pharyngitis.

Oral Temperature (Norm 36.9): 36.9

Physical Signs of CFS/ME (see Ch. 5)

Thoracic Spine: slight tender mid-segments; Flattened upper segments; Kyphotic lower segments.

Breast tissue: Varicose Lymph and tenderness bilaterally; Perrin's point +ve

Coeliac plexus region: Tender

Cranial Flow (Involuntary mechanism): Lower than normal.

## APPENDIX A6: Self report questionnaires

Questionnaire No.1.GENERAL HEALTH QUESTIONNAIRE (Perrin *et al.*, 1998)

SUBJECT NO.

_ _ _ _

**6. PLEASE INDICATE THE SEVERITY OF THE DIFFERENT COMPLAINTS THAT YOU HAVE BEEN SUFFERING FROM DURING THIS PAST WEEK;**

**WHERE:-**

**1. = NO PROBLEM WITH THIS COMPLAINT.**

**2. = SLIGHT PROBLEM WITH THIS COMPLAINT.**

**3. = FAIRLY SEVERE.**

**4.= VERY SEVERE.**

**a ) MILD RECURRENT FEVERS** ☐

**b) SORE THROAT** ☐

**c) PHYSICAL WEAKNESS** ☐

**d) NAUSEA** ☐

**e) PROLONGED FATIGUE AFTER EXERCISE** ☐

**f) HEADACHE** ☐

**g) EAR ACHE** ☐

**h) IRRITABLE BOWEL** ☐

**i) MUSCLE PAIN IN ARMS AND LEGS** ☐

**j) PAIN IN CHEST** ☐

**k) PAINFUL JOINTS** ☐

**l) FEELING HOT/COLD** ☐

**m) SWEATING** ☐

**n) SHIVERING** ☐

**o) DISTURBED SLEEP** ☐

**p) RACING HEART** ☐

**FORM Q/OST/M.E. 1..**
**DATE _ _:_ _:_ _**

**1.**

SUBJECT NO.

_____

QUESTION 6. CONT.

q) PAIN IN NECK ☐

r) PAIN IN SHOULDERS ☐

s) PAIN IN BACK ☐

t) SENSITIVE TO LIGHT ☐

u) SENSITIVE TO SOUND ☐

v) DEPRESSED ☐

w FEELINGS OF ANXIETY/PANIC ☐

x) LOSS OF CONCENTRATION ☐

y) LOSS OF MEMORY ☐

z) ALLERGIES ☐

N.B. WHERE:-

1. = NO PROBLEM WITH THIS COMPLAINT.

2. = SLIGHT PROBLEM WITH THIS COMPLAINT.

3. = FAIRLY SEVERE

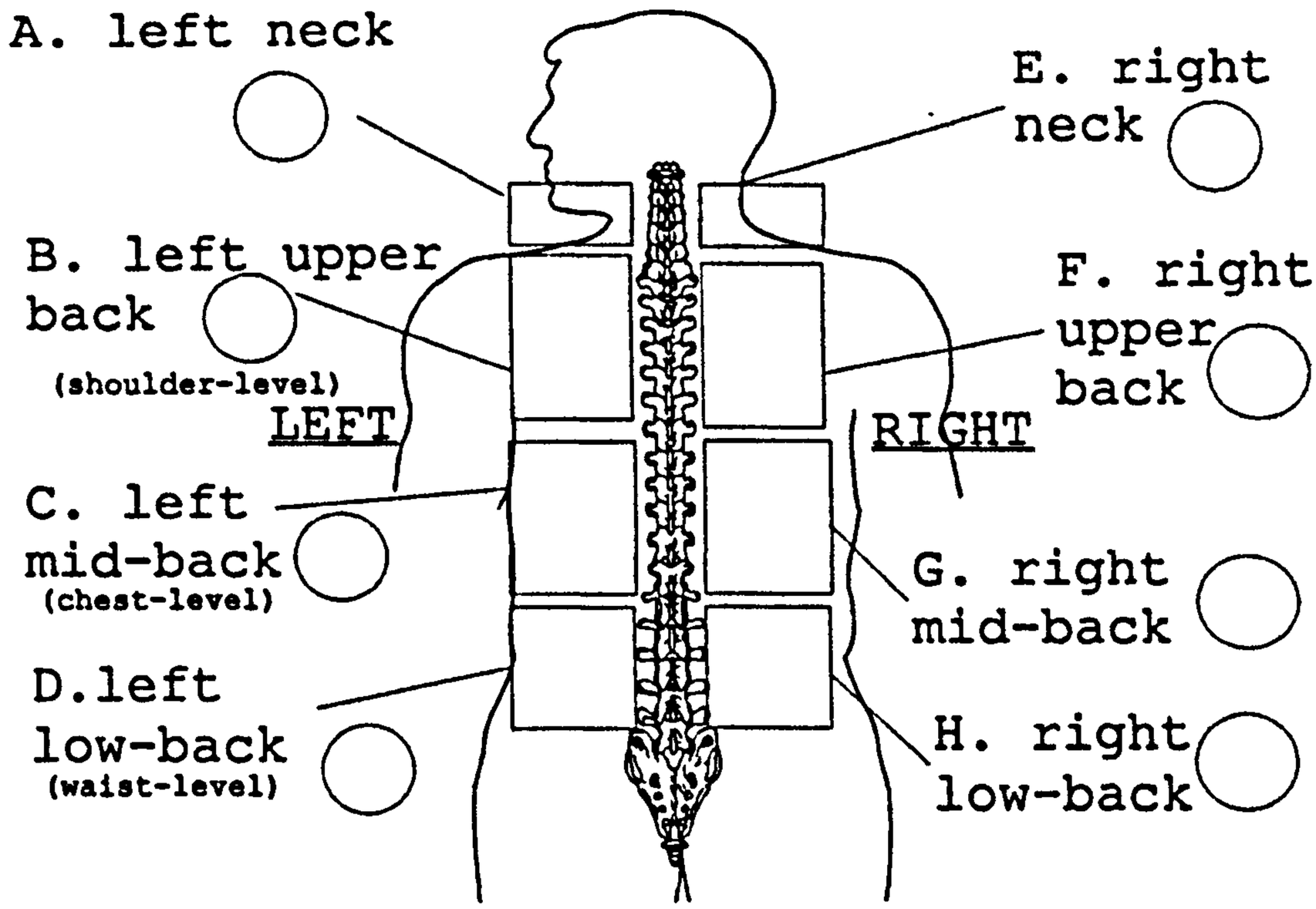
4.= VERY SEVERE.

IF YOU ARE SUFFERING FROM ANY OTHER COMPLAINT, PLEASE SPECIFY IN THE SPACE PROVIDED BELOW.

Questionnaire No. 2. BACK PAIN (Perrin *et al.*, 1998)

SUBJECT NO. FORM Q/OST/M.E. 2.1

## BACK SYMPTOMS




Please indicate the region/s of pain on the above diagram by placing a score in the relevant circle.

Where: ① = no discomfort (pain-free)
② = slight discomfort
③ = moderate pain
④ = severe pain

## BACK SYMPTOMS cont.

SUBJECT NO. FORM Q/OST/M.E.2.2

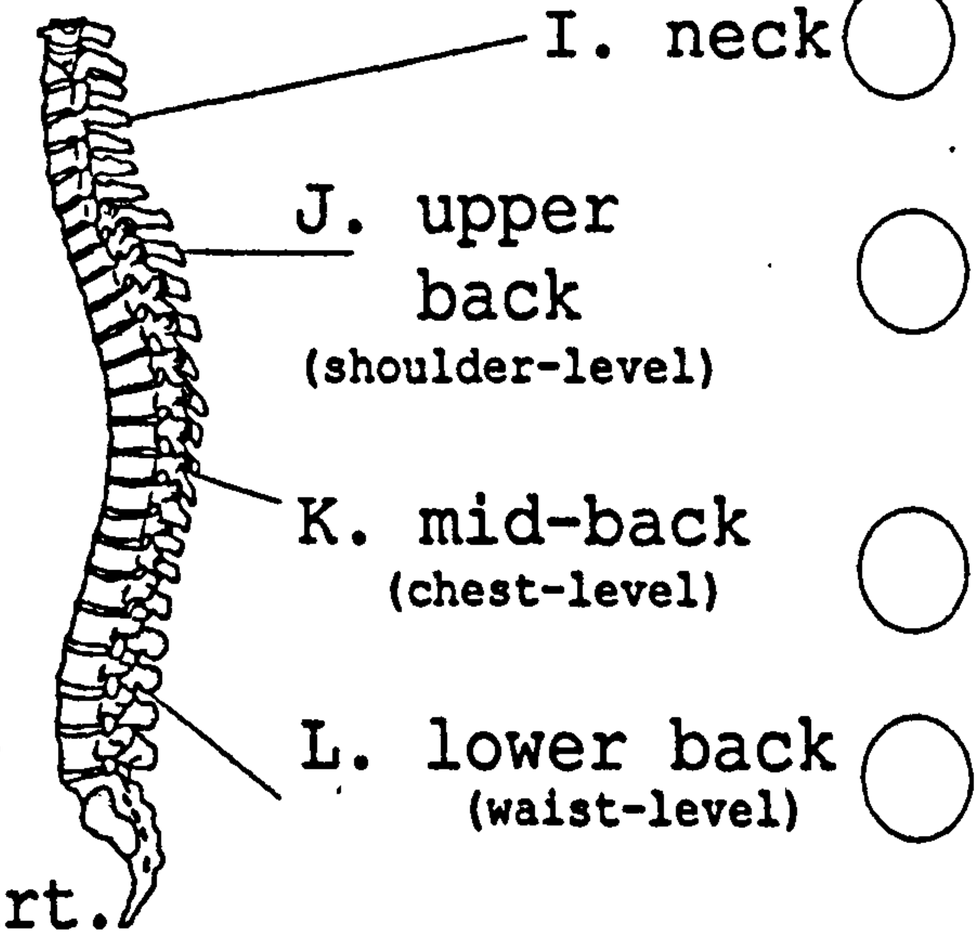
---

Please indicate the region/s of pain, in the spine, on the below diagram by placing a score in the relevant circle.

Where:
① = no discomfort(pain-free)
② = slight discomfort
③ = moderate pain
④ = severe pain

SIDE VIEW

**N.B.** This section only applies to any central pain felt on the actual spinal column. Any pain at the side of the spine should be recorded in the previous chart.




Date: _ _ _ _ _ _

Questionnaire No. 3. THE REVISED BECK DEPRESSION INVENTORY (Beck *et al.*, 1979)

**Instructions:** On this questionnaire are groups of statements. Please read each group of statements carefully. Then circle the statement in each group which best describes the way you have been feeling in the last week, including today! Circle the number beside the statement you have picked. If several statements in the group seem to apply equally well, circle each one. **Be sure to read all the statements in each group before making your choice.**

1. 0= I do not feel sad.
   1= I feel sad.
   2= I am sad all of the time and I can't snap out of it.
   3= I am so sad or unhappy that I can't stand it.

2. 0= I am not particularly discouraged about the future.
   1= I feel discouraged about the future.
   2= I feel that I have nothing to look forward to.
   3= I feel that the future is hopeless and that things cannot improve.

3. 0= I do not feel like a failure.
   1= I feel I have failed more than the average person.
   2= As I look back on my life, all I can see is a lot of failures.
   3= I feel I am a complete failure as a person.

4. 0= I get as much satisfaction out of things as I used to.
   1= I don't enjoy things the way I used to.
   2= I don't get real satisfaction out of anything anymore.
   3= I am dissatisfied or bored with everything.

5. 0= I don't feel particularly guilty.
   1= I feel guilty a good part of the time.
   2= I feel quite guilty most of the time.
   3= I feel guilty all of the time.

6. 0= I don't feel I am being punished.
   1= I feel I may be punished.
   2= I expect to be punished.
   3= I feel I am being punished.

7. 0= I don't feel disappointed in myself.
   1= I am disappointed in myself.
   2= I am disgusted with myself.
   3= I hate myself.

8. 0=I don't feel I am any worse than anybody else.
   1= I am critical of myself for my weaknesses and mistakes.
   2= I blame myself for all my faults.
   3= I blame myself for everything bad that happens.

9. 0= I don't have any thoughts of killing myself.
   1= I have thoughts of killing myself, but I would never carry them out.
   2= I would like to kill myself.
   3= I would kill myself if I had the chance.

10. 0= I don't cry any more than usual.
    1= I cry more than I used to.
    2= I cry all the time now.
    3= I used to be able to cry, but now I can't cry even though I want to.

11. 0= I am no more irritated now than I ever am.
    1= I get annoyed or irritated more easily than I used to.
    2= I feel irritated all the time now.
    3= I don't get irritated at all by the things that used to irritate me.

12. 0= I have not lost interest in other people.
    1= I am less interested in other people than I used to be.
    2= I have lost most of my interest in other people.
    3= I have lost all of my interest in other people.

13. 0= I make decisions about as well as I ever could.
1= I put off making decisions more than I used to.
2= I have greater difficulty in making decisions than before.
3= I can't make decisions at all anymore.

14. 0= I don't feel I look any worse than I used to.
1= I am worried that I am looking old or unattractive.
2= I feel that there are permanent changes in my appearance that make me look unattractive.
3= I believe that I look ugly.

15. 0= I can work about as well as before.
1= It takes an extra effort to get started at doing something.
2= I have to push myself very hard to do anything.
3= I can't do any work at all.

16. 0= I can sleep as well as usual.
1= I don't sleep as well as I used to.
2= I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.
3= I wake up several hours earlier than I used to and cannot get back to sleep.

17. 0= I don't get more tired than usual.
1= I get tired more easily than I used to.
2= I get tired from doing almost anything.
3= I am too tired to do anything.

18. 0= My appetite is no worse than usual.
1= My appetite is not as good as it used to be.
2= My appetite is much worse now.
3= I have no appetite at all anymore.

19. 0= I haven't lost much weight, if any, lately.
1= I have lost more than 5 pounds. •••
2= I have lost more than 10 pounds. •••
3= I have lost more than 15 pounds. •••
••• I am purposely trying to lose weight by eating less . Yes___ No___

20. 0= I am no more worried about my health than usual.
1= I am worried about physical problems such as aches and pains; or upset stomach; or constipation.
2= I am very worried about physical problems and it's hard to think of much else.
3= I am so worried about my physical problems that I cannot think of anything else.

21. 0= I have not noticed any recent change in my interest in sex.
1= I am less interested in sex than I used to be.
2= I am much less interested in sex now.
3= I have lost interest in sex completely.

Questionnaire No. 4. THE BECK ANXIETY INVENTORY (Beck *et al.*, 1988).

CODE NUMBER ___ ___ ___ ___

# QUESTIONNAIRE Q/OST/M.E. 4.

PLEASE CAREFULLY READ EACH ITEM IN THE LIST BELOW. INDICATE HOW MUCH YOU HAVE BEEN BOTHERED BY EACH SYMPTOM DURING THE PAST WEEK, INCLUDING TODAY BY PLACING A SCORE IN THE CORRESPONDING BOX.

WHERE 0 = NOT AT ALL

1 = MILDLY (it did not bother me much)

2 = MODERATELY (It was very unpleasant but I could stand it.)

3 = SEVERELY (I could barely stand it)

1. Numbness or tingling ☐
2. Feeling hot ☐
3 Wobbliness in legs ☐
4 Unable to relax ☐
5. Fear the worst happening ☐
6 Dizzy or lightheaded ☐
7. Heart pounding or racing ☐
8 Unsteady ☐
9. Terrified ☐
10 Nervous ☐
11. Feelings of choking ☐
12. Hands trembling ☐
13 Shaky ☐

FORM Q/OST/M.E. 4. 1.
DATE ___/___/___

CODE NUMBER ___ ___ ___ ___

NB 0 = NOT AT ALL

1 = MILDLY(it did not bother me much)

2 = MODERATELY(It was very unpleasant but I could stand it.)

3 = SEVERELY (I could barely stand it)

14 Fear of losing control ☐

15. Difficulty breathing ☐

16. Fear of Dying ☐

17. Scared ☐

18 Indigestion or discomfort in abdomen ☐

19. Faint ☐

20. Face flushed ☐

21. Sweating(not due to heat) ☐

Thank you for completing this form. Please check that you have filled in all your replies, correctly

Questionnaire No.5.THE MORGAN-GLEDHILL SLEEP QUESTIONNAIRE (Tomeny and Morgan, 1990)

**Scoring system is outlined in red.**



M.E. RESEARCH PROJECT
SLEEP QUESTIONNAIRE

CODE NUMBER: _ _ _ _ DATE: __:__:__

Below are some questions concerning your sleep at night. please answer all the questions. If your times for going to bed and so vary greatly, give ranges (e.g.. 10-11pm, 30-60 mins).

| | |
|---|---|
| 1 | For how long do you usually sleep at night? Compare with sleep/age norms |
| 2 | After settling down, how long does it usually take you to fall asleep? Divide minutes by 10 |
| 3 | How often do you wake up too early in the morning? (tick one): Score<br>Never ☐<br>Seldom ☐<br>Sometimes ☐<br>Often ☐<br>All the time ☐ |

Never = 0 to All the time = 4

# M.E. RESEARCH PROJECT
## SLEEP QUESTIONNAIRE

CODE NUMBER: _ _ _ _ DATE: __ : __ : __

| | | |
|---|---|---|
| 4 | Do you usually wake up during the night? (tick one): | Yes ☐1<br>No ☐0 |
| 5 | If Yes: What usually awakes you? (answer in your own words) | |
| 6 | How many times (on average) do you awake each night? | Score 1 for each time |
| 7 | For how long are you awake on each of these occasions? | Score 1 for each hour |
| 8 | At what time do you usually go to bed?<br>Check difference of Q.9 - Q.8 with Q.1 | |
| 9 | At what time do you usually wake up (in the morning)? | |

# M.E. RESEARCH PROJECT
## SLEEP QUESTIONNAIRE

CODE NUMBER: _ _ _ _ _

DATE: __:__:__

| | | |
|---|---|---|
| 10 | At what time do you usually get up? | |
| 11 | How refreshed do you usually feel when you wake up in the morning (tick one)? | Score: very refreshed = 0<br>Very refreshed ☐<br>Quite refreshed ☐<br>Unrefreshed ☐<br>Tired ☐<br>Shattered ☐<br>~~shattered = 1~~ |
| 12 | In general, how much sleep do you think a person your age needs? | |
| 13 | How long have you had your present sleep problem | |
| 14 | What do you think is the cause of your present sleep problem? | |
| 15 | Have you ever had serious trouble with your sleep in the past? | Yes ☐<br>No ☐ |

# M.E. RESEARCH PROJECT
# SLEEP QUESTIONNAIRE

CODE NUMBER: _ _ _ _ DATE: __:__:__

16 Have you gained or lost weight in the last few months? (tick one)

- Yes, I have gained weight ☐
- Yes, I have lost weight ☐
- No, I'm about the same ☐

17 Sub-score from 0=very good sleeper to 4 = very poor sleeper

Before the present problem how would you have described yourself? (tick one)

- A very good sleeper ☐
- A good sleeper ☐
- An average sleeper ☐
- A poor sleeper ☐
- A very poor sleeper ☐

18 Sub-score from 0=very good sleeper to 4 = very poor sleeper

How would you describe yourself now?

- A very good sleeper ☐
- A good sleeper ☐
- An average sleeper ☐
- A poor sleeper ☐
- A very poor sleeper ☐

Score difference of Q.18 – Q.17

19 Do you usually take a nap during the day? Yes ☐ No ☐

Score yes = 1 no = 0

20 When do usually nap? (give length of each nap) ☐

**Use sleep/age norms with answer in Q. 1.**

**Score 1 for each hour difference.**

# SLEEP/ AGE NORMS

| AGE | | HOURS of SLEEP |
|---|---|---|
| 19 - 30 | = | 7.75 |
| 33-45 | = | 7 |
| 50 | = | 6 |
| 90 | = | 5.75 |

Source: Revised by Roffwarg et al since publication in Science, Vol 152 (1966) pp. 604-19.

## Questionnaire No. 6. BROADBENT'S COGNITIVE FUNCTION QUESTIONNAIRE (Broadbent *et al.*, 1982)

**CFQ**

The following questions are about minor mistakes which everyone makes from time to time, but some of which happen more often than others. We want to know how often these things have happened to you in the last six months. Please circle the appropriate number.

| | | very often | quite often | occas-ionally | very rarely | never |
|---|---|---|---|---|---|---|
| 1. | Do you read something and find you haven't been thinking about it and must read it again? | 4 | 3 | 2 | 1 | 0 |
| 2. | Do you find you forget why you went from one part of the house to the other? | 4 | 3 | 2 | 1 | 0 |
| 3. | Do you fail to notice sign-posts on the road? | 4 | 3 | 2 | 1 | 0 |
| 4. | Do you find that you confuse right and left when giving directions? | 4 | 3 | 2 | 1 | 0 |
| 5. | Do you bump into people? | 4 | 3 | 2 | 1 | 0 |
| 6. | Do you find that you forget whether you've turned off a light or a fire or locked the door? | 4 | 3 | 2 | 1 | 0 |
| 7. | Do you fail to listen to people's names when you are meeting them? | 4 | 3 | 2 | 1 | 0 |
| 8. | Do you say something and realise afterwards that it might be taken as insulting? | 4 | 3 | 2 | 1 | 0 |
| 9. | Do you fail to hear people speaking to you when you are doing something else? | 4 | 3 | 2 | 1 | 0 |
| 10. | Do you lose your temper and then regret it? | 4 | 3 | 2 | 1 | 0 |

| | | very often | quite often | occas-ionally | very rarely | never |
|---|---|---|---|---|---|---|
| 11. | Do you leave important letters unanswered for days? | 4 | 3 | 2 | 1 | 0 |
| 12. | Do you find you forget which way to turn on a road you know well but rarely use? | 4 | 3 | 2 | 1 | 0 |
| 13. | Do you fail to see what you want in a supermarket (although it's there)? | 4 | 3 | 2 | 1 | 0 |
| 14. | Do you find yourself suddenly wondering whether you've used a word correctly? | 4 | 3 | 2 | 1 | 0 |
| 15. | Do you have trouble making your mind? | 4 | 3 | 2 | 1 | 0 |
| 16. | Do you forget appointments? | 4 | 3 | 2 | 1 | 0 |
| 17. | Do you forget where you put something like a newspaper or a book? | 4 | 3 | 2 | 1 | 0 |
| 18. | Do you find you accidentally throw away the thing you want and keep what you meant to throw away - as in the example of throwing away the matchbox and putting the used match in your pocket? | 4 | 3 | 2 | 1 | 0 |
| 19. | Do you daydream when you ought to be listening to something? | 4 | 3 | 2 | 1 | 0 |
| 20. | Do you find you forget people's names? | 4 | 3 | 2 | 1 | 0 |
| 21. | Do you start doing one thing at home and get distracted into doing something else (unintentionally)? | 4 | 3 | 2 | 1 | 0 |

| | | very often | quite often | occas-ionally | very rarely | never |
|---|---|---|---|---|---|---|
| 22. | Do you find something you can't quite remember something although it's "on the tip of you tongue"? | 4 | 3 | 2 | 1 | 0 |
| 23. | Do you find that you forget what you came to the shops to buy? | 4 | 3 | 2 | 1 | 0 |
| 24. | Do you drop things? | 4 | 3 | 2 | 1 | 0 |
| 25. | Do you find you can't think of anything to say? | 4 | 3 | 2 | 1 | 0 |

Questionnaire No. 7.THE NOTTINGHAM HEALTH QUESTIONNAIRE

Score: YES = 1 NO = 2 (Hunt *et al.*,1981)

Please not wr: in thi; margin

LISTED BELOW ARE SOME PROBLEMS PEOPLE MIGHT HAVE IN THEIR DAILY LIVES.

READ THE LIST CAREFULLY AND PUT A TICK IN THE BOX ☐ UNDER YES FOR ANY PROBLEM THAT APPLIES TO YOU AT THE MOMENT. TICK THE BOX UNDER NO FOR ANY PROBLEM THAT DOES NOT APPLY TO YOU.

PLEASE ANSWER EVERY QUESTION. IF YOU ARE NOT SURE WHETHER TO ANSWER YES OR NO, TICK WHICHEVER ANSWER YOU THINK IS MOST TRUE AT THE MOMENT.

| | YES | NO |
|---|---|---|
| I'm tired all the time | ☐ | ☐ |
| I have pain at night | ☐ | ☐ |
| Things are getting me down | ☐ | ☐ |

| | YES | NO |
|---|---|---|
| I have unbearable pain | ☐ | ☐ |
| I take tablets to help me sleep | ☐ | ☐ |
| I've forgotten what it's like to enjoy myself | ☐ | ☐ |

| | YES | NO |
|---|---|---|
| I'm feeling on edge | ☐ | ☐ |
| I find it painful to change position | ☐ | ☐ |
| I feel lonely | ☐ | ☐ |

Please turn over

1

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in th
margi

| | YES | NO |
|---|---|---|
| I can only walk about indoors | ☐ | ☐ |
| I find it hard to bend | ☐ | ☐ |
| Everything is an effort | ☐ | ☐ |

| | YES | NO |
|---|---|---|
| I'm waking up in the early hours of the morning | ☐ | ☐ |
| I'm unable to walk at all | ☐ | ☐ |
| I'm finding it hard to make contact with people | ☐ | ☐ |

REMEMBER IF YOU ARE NOT SURE WHETHER TO ANSWER 'YES' OR 'NO' TO A PROBLEM, TICK WHICHEVER ANSWER YOU THINK MORE TRUE AT THE MOMENT.

| | YES | NO |
|---|---|---|
| The days seem to drag | ☐ | ☐ |
| I have trouble getting up and down stairs or steps | ☐ | ☐ |
| I find it hard to reach for things | ☐ | ☐ |

| | YES | NO |
|---|---|---|
| I'm in pain when I walk | ☐ | ☐ |
| I lose my temper easily these days | ☐ | ☐ |
| I feel there is nobody I am close to | ☐ | ☐ |

Please turn over

| | YES | NO |
|---|---|---|
| I lie awake for most of the night | ☐ | ☐ |
| I feel as if I'm losing control | ☐ | ☐ |
| I'm in pain when I'm standing | ☐ | ☐ |

| | YES | NO |
|---|---|---|
| I find it hard to dress myself | ☐ | ☐ |
| I soon run out of energy | ☐ | ☐ |
| I find it hard to stand for long (eg at the kitchen sink, waiting for a bus) | ☐ | ☐ |

| | YES | NO |
|---|---|---|
| I'm in constant pain | ☐ | ☐ |
| It takes me a long time to get to sleep | ☐ | ☐ |
| I feel I am a burden to people | ☐ | ☐ |

| | YES | NO |
|---|---|---|
| Worry is keeping me awake at night | ☐ | ☐ |
| I feel that life is not worth living | ☐ | ☐ |
| I sleep badly at night | ☐ | ☐ |

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| | YES | NO |
|---|---|---|
| I'm finding it hard to get on with people | ☐ | ☐ |
| I need help to walk about outside (eg a walking aid or someone to support me) | ☐ | ☐ |

| | YES | NO |
|---|---|---|
| I'm in pain when going up and down stairs or steps | ☐ | ☐ |
| I wake up feeling depressed | ☐ | ☐ |
| I'm in pain when I'm sitting | ☐ | ☐ |

NOW PLEASE GO BACK TO PAGE 1 AND MAKE SURE THAT YOU HAVE ANSWERED 'YES' OR 'NO' TO EVERY QUESTION, ON ALL FOUR PAGES OF THE QUESTIONNAIRE.

THANK YOU FOR YOUR HELP

Questionnaire No. 8.

## THE PROFILE OF FATIGUE RELATED STATES (Ray *et al.*, 1992)

### PFRS

Below is a list of problems which may or may not apply to you. For each problem, please say to what extent you have experienced this during the PAST WEEK (including today). Do not think for too long before answering but give your immediate reaction. Please be careful not to miss out any of the items. Remember, we are talking about the past week and not your illness in general. Give your answer by circling any number from 1 to 7 to the right of the item, where:

1 = not at all
4 = moderately
7 = extremely

| | | |
|---|---|---|
| 1. | Feeling physically tired even when taking things easy. | 1 2 3 4 5 6 7 |
| 2. | Your limbs feeling heavy. | 1 2 3 4 5 6 7 |
| 3. | Getting easily upset by things. | 1 2 3 4 5 6 7 |
| 4. | Difficulty concentrating. | 1 2 3 4 5 6 7 |
| 5. | Stomach pain. | 1 2 3 4 5 6 7 |
| 6. | Not having the physical energy to do anything. | 1 2 3 4 5 6 7 |
| 7. | Difficulty standing for long. | 1 2 3 4 5 6 7 |
| 8. | Losing your temper easily. | 1 2 3 4 5 6 7 |
| 9. | Difficulty remembering things. | 1 2 3 4 5 6 7 |
| 10. | Muscles feel weak even after resting. | 1 2 3 4 5 6 7 |
| 11. | Feeling depressed. | 1 2 3 4 5 6 7 |
| 12. | Muscles tender to the touch. | 1 2 3 4 5 6 7 |
| 13. | Slowness of thought. | 1 2 3 4 5 6 7 |
| 14. | Tremor or twitching. | 1 2 3 4 5 6 7 |
| 15. | The slightest exercise making you physically tired. | 1 2 3 4 5 6 7 |
| 16. | Being irritable | 1 2 3 4 5 6 7 |
| 17. | Difficulty reasoning things out. | 1 2 3 4 5 6 7 |

1 = not at all
4 = moderately
7 = extremely

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| 18. | Burning, tingling or crawling sensations. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 19. | Numbness in some part of your body | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 20. | Back pain. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 21. | Feeling anxious. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 22. | A feeling of confusion ("mental fog"). | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 23. | Bouts of sweating (day or night). | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 24. | Feeling physically drained. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 25. | Dizziness or giddiness. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 26. | Absent-mindedness. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 27. | Worrying about things that do not matter. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 28. | Feeling physically tired even after a good night's sleep. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 29. | Difficulty understanding e g. what someone was saying to you. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 30. | Feeling pessimistic about the future. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 31. | Cold hands or feet. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 32. | Having to stop doing something, that was easy in itself, because it made you tired. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 33. | Muscles feeling weak after slight exercise. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 34. | Difficulty following things e g. a simple plot on TV. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 35. | Hot or cold spells. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 36. | Feeling tense. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |
| 37. | Feeling faint. | 1 | 2 | 3 | 4 | 5 | 6 | 7 |

1 = not at all
4 = moderately
7 = extremely

| | | |
|---|---|---|
| 38. | Difficulty finding the right word | 1 2 3 4 5 6 7 |
| 39. | Feeling chilled or shivery. | 1 2 3 4 5 6 7 |
| 40. | Tearfulness. | 1 2 3 4 5 6 7 |
| 41. | Irregular or rapid heartbeats. | 1 2 3 4 5 6 7 |
| 42. | Feeling worthless. | 1 2 3 4 5 6 7 |
| 43. | Forgetting what you were trying to say. | 1 2 3 4 5 6 7 |
| 44. | Being easily angered when things went wrong. | 1 2 3 4 5 6 7 |
| 45. | Feeling mentally tired even after a good night's sleep. | 1 2 3 4 5 6 7 |
| 46. | Diarrhoea or constipation. | 1 2 3 4 5 6 7 |
| 47. | Feeling nervous. | 1 2 3 4 5 6 7 |
| 48. | Feeling sad. | 1 2 3 4 5 6 7 |
| 49. | The slightest effort making you mentally tired. | 1 2 3 4 5 6 7 |
| 50. | Feeling like you had a temperature. | 1 2 3 4 5 6 7 |
| 51. | Other people annoying you. | 1 2 3 4 5 6 7 |
| 52. | A sore throat. | 1 2 3 4 5 6 7 |
| 53. | Feelings of resentment. | 1 2 3 4 5 6 7 |
| 54. | Being slow to react. | 1 2 3 4 5 6 7 |

**APPENDIX A7: The Borg Scale of Perceived Exertion**

(Borg and Linderholm, 1970)

# BORG SCALE OF PERCEIVED EXERTION

## Test no:

## Code no: _ _ _ _

**Please rate how much strain you are under doing this exercise.**

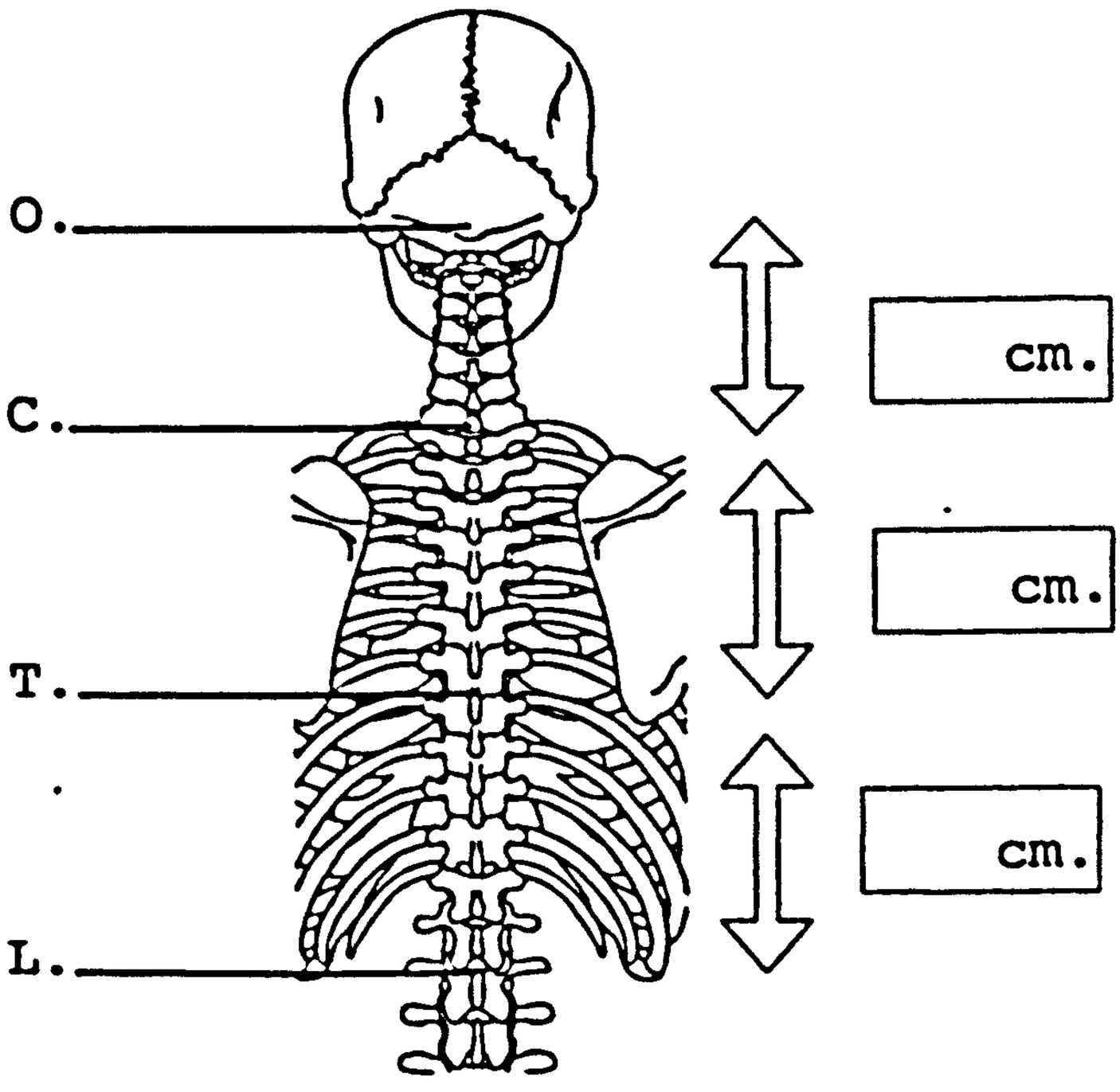
| | |
|---|---|
| 6 | |
| 7 | **Very, very light** |
| 8 | |
| 9 | **Very light** |
| 10 | |
| 11 | **Fairly light** |
| 12 | |
| 13 | **Somewhat hard** |
| 14 | |
| 15 | **Hard** |
| 16 | |
| 17 | **Very hard** |
| 18 | |
| 19 | **Very, very hard** |
| 20 | |

**THANK YOU!**

## APPENDIX A8: Probe Position Calibration Chart

Calibration chart for the postioning of probes used in spinal movement analysis (phase 1 of study).

# PROBE POSITIONS




CODE NO. __ : __ : __ : __

## APPENDIX A9: Statistical analysis of questionnaires (phase 1)

The full statistical analysis of individual subject's score of each group and at each stage of the year's trial above using two-sample t tests on the reductions in scores from start to months 3, 6, 9 and 12 . Statistical software package used: SPSS for Windows.

The most important statistic from each test is the p-value, which is 0.180 for the first test, and so on. Those tests with $p<0.05$ indicate significant differences between the mean reductions of the control group and the patient group at the 5% level of significance.

### Health

**Two-Sample T-Test and CI: Health Q1_s-3, group**

Two-sample T for Health Q1_s-3

| group | N | Mean | St. Dev | SE Mean |
|---|---|---|---|---|
| 1 | 24 | 2.38 | 6.44 | 1.3 |
| 2 | 34 | 5.7 | 10.7 | 1.8 |

Difference = μ (1) – μ (2)

Estimate for difference: -3.33

95% CI for difference: (-8.25, 1.59)

T-Test of difference = 0 (vs not =): T-Value = -1.36 p-value = 0.180 DF = 56

Both use Pooled St. Dev = 9.21

**Two-Sample T-Test and CI: Health Q1_s-6, group**

Two-sample T for Health Q1_s-6

| group | N | Mean | St. Dev | SE Mean |
|---|---|---|---|---|
| 1 | 24 | 2.00 | 6.98 | 1.4 |
| 2 | 33 | 10.3 | 10.8 | 1.9 |

Difference = μ (1) – μ(2)

Estimate for difference: -8.30

95% CI for difference: (-13.36, -3.25)

T-Test of difference = 0 (vs not =): T-Value = -3.29 p-value = 0.002 DF = 55

Both use Pooled St. Dev = 9.40

**Two-Sample T-Test and CI: Health Q1_s-9, group**

Two-sample T for Health Q1_s-9

| group | N | Mean | St. Dev | SE Mean |
|---|---|---|---|---|
| 1 | 24 | 0.88 | 7.38 | 1.5 |
| 2 | 33 | 11.12 | 9.77 | 1.7 |

Difference = μ (1) – μ (2)

Estimate for difference: -10.25

95% CI for difference: (-15.00, -5.49)

T-Test of difference = 0 (vs not =): T-Value = -4.32 p-value = 0.000 DF = 55

Both use Pooled St. Dev = 8.85

**Two-Sample T-Test and CI: Health Q1_s-12, group**

Two-sample T for Health Q1_s-12

| group | N | Mean | St. Dev | SE Mean |
|---|---|---|---|---|
| 1 | 24 | -1.79 | 8.07 | 1.6 |
| 2 | 33 | 13.5 | 10.5 | 1.8 |

Difference = μ (1) – μ (2)

Estimate for difference: -15.25

95% CI for difference: (-20.37, -10.12)

T-Test of difference = 0 (vs not =): T-Value = -5.96 p-value = 0.000 DF = 55

Both use Pooled St. Dev = 9.53

## Back Pain

### Two-Sample T-Test and CI: Back Q2_s-3, group

Two-sample T for Back Q2_s-3

| group | N | Mean | St. Dev | SE Mean |
|---|---|---|---|---|
| 1 | 24 | -0.50 | 5.18 | 1.1 |
| 2 | 34 | 2.21 | 7.98 | 1.4 |

Difference = μ (1) – μ (2)

Estimate for difference: -2.71

95% CI for difference: (-6.42, 1.01)

T-Test of difference = 0 (vs not =): T-Value = -1.46 p-value = 0.151 DF = 56

Both use Pooled St. Dev = 6.96

### Two-Sample T-Test and CI: Back Q2_s-6, group

Two-sample T for Back Q2_s-6

| group | N | Mean | St. Dev | SE Mean |
|---|---|---|---|---|
| 1 | 24 | -0.29 | 4.96 | 1.0 |
| 2 | 33 | 4.67 | 7.19 | 1.3 |

Difference = μ (1) – μ (2)

Estimate for difference: -4.96

95% CI for difference: (-8.38, -1.54)

T-Test of difference = 0 (vs not =): T-Value = -2.91 p-value = 0.005 DF = 55

Both use Pooled St. Dev = 6.36

**Two-Sample T-Test and CI: Back Q2_s-9, group**

Two-sample T for Back Q2_s-9

| group | N | Mean | St. Dev | SE Mean |
|---|---|---|---|---|
| 1 | 24 | -0.92 | 4.57 | 0.93 |
| 2 | 33 | 5.39 | 6.86 | 1.2 |

Difference = μ (1) – μ (2)

Estimate for difference: -6.31

95% CI for difference: (-9.54, -3.08)

T-Test of difference = 0 (vs not =): T-Value = -3.91 p-value = 0.000 DF = 55

Both use Pooled St. Dev = 6.01

**Two-Sample T-Test and CI: Back Q2_s-12, group**

Two-sample T for Back Q2_s-12

| group | N | Mean | St. Dev | SE Mean |
|---|---|---|---|---|
| 1 | 24 | -0.83 | 6.27 | 1.3 |
| 2 | 33 | 5.55 | 8.00 | 1.4 |

Difference = μ (1) – μ (2)

Estimate for difference: -6.38

95% CI for difference: (-10.32, -2.44)

T-Test of difference = 0 (vs not =): T-Value = -3.24 p-value = 0.002 DF = 55

Both use Pooled St. Dev = 7.33

## Depression

### Two-Sample T-Test and CI: BDI Q3_s-3, group

Two-sample T for BDI Q3_s-3

| group | N | Mean | St. Dev | SE Mean |
|---|---|---|---|---|
| 1 | 24 | 1.00 | 4.77 | 0.97 |
| 2 | 34 | 4.06 | 5.03 | 0.86 |

Difference = μ (1) – μ (2)

Estimate for difference: -3.06

95% CI for difference: (-5.69, -0.43)

T-Test of difference = 0 (vs not =): T-Value = -2.33 p-value = 0.023 DF = 56

Both use Pooled St. Dev = 4.92

### Two-Sample T-Test and CI: BDI Q3_s-6, group

Two-sample T for BDI Q3_s-6

| group | N | Mean | St. Dev | SE Mean |
|---|---|---|---|---|
| 1 | 24 | 3.58 | 4.69 | 0.96 |
| 2 | 33 | 6.73 | 5.79 | 1.0 |

Difference = μ(1) – μ(2)

Estimate for difference: -3.14

95% CI for difference: (-6.03, -0.26)

T-Test of difference = 0 (vs not =): T-Value = -2.19 p-value = 0.033 DF = 55

Both use Pooled St. Dev = 5.36

**Two-Sample T-Test and CI: BDI Q3_s-9, group**

Two-sample T for BDI Q3_s-9

| group | N | Mean | St. Dev | SE Mean |
|---|---|---|---|---|
| 1 | 24 | 2.79 | 6.02 | 1.2 |
| 2 | 33 | 8.00 | 6.44 | 1.1 |

Difference = μ(1) – μ(2)

Estimate for difference: -5.21

95% CI for difference: (-8.58, -1.84)

T-Test of difference = 0 (vs not =): T-Value = -3.10 p-value = 0.003 DF = 55

Both use Pooled St. Dev = 6.27

**Two-Sample T-Test and CI: BDI Q3_s-12, group**

Two-sample T for BDI Q3_s-12

| group | N | Mean | St. Dev | SE Mean |
|---|---|---|---|---|
| 1 | 24 | 1.75 | 6.14 | 1.3 |
| 2 | 33 | 8.03 | 6.05 | 1.1 |

Difference = μ(1) – μ(2)

Estimate for difference: -6.28

95% CI for difference: (-9.55, -3.01)

T-Test of difference = 0 (vs not =): T-Value = -3.85 p-value = 0.000 DF = 55

Both use Pooled St. Dev = 6.09

## Anxiety

**Two-Sample T-Test and CI: BAI Q4_s-3, group**

**Two-sample T for BAI Q4_s-3**

| group | N | Mean | St. Dev | SE Mean |
|---|---|---|---|---|
| 1 | 24 | 0.50 | 7.31 | 1.5 |
| 2 | 34 | 5.00 | 7.15 | 1.2 |

Difference = μ(1) – μ(2)

Estimate for difference: -4.50

95% CI for difference: (-8.35, -0.65)

T-Test of difference = 0 (vs not =): T-Value = -2.34 p-value = 0.023 DF = 56

Both use Pooled St. Dev = 7.21

**Two-Sample T-Test and CI: BAI Q4_s-6, group**

**Two-sample T for BAI Q4_s-6**

| group | N | Mean | St. Dev | SE Mean |
|---|---|---|---|---|
| 1 | 24 | -0.83 | 6.38 | 1.3 |
| 2 | 33 | 5.73 | 6.80 | 1.2 |

Difference = μ(1) – μ(2)

Estimate for difference: -6.56

95% CI for difference: (-10.12, -3.00)

T-Test of difference = 0 (vs not =): T-Value = -3.69 p-value = 0.001 DF = 55

Both use Pooled St. Dev = 6.63

**Two-Sample T-Test and CI: BAI Q4_s-9, group**

**Two-sample T for BAI Q4_s-9**

| group | N | Mean | St. Dev | SE Mean |
|---|---|---|---|---|
| 1 | 24 | -0.42 | 6.52 | 1.3 |
| 2 | 33 | 7.97 | 6.73 | 1.2 |

Difference = μ(1) – μ(2)

Estimate for difference: -8.39

95% CI for difference: (-11.96, -4.81)

T-Test of difference = 0 (vs not =): T-Value = -4.70 p-value = 0.000 DF = 55

Both use Pooled St. Dev = 6.65

MTB > TwoT 'BAI Q4_s-12' 'group';

SUBC> Pooled.

**Two-Sample T-Test and CI: BAI Q4_s-12, group**

**Two-sample T for BAI Q4_s-12**

| group | N | Mean | St. Dev | SE Mean |
|---|---|---|---|---|
| 1 | 24 | -1.71 | 8.23 | 1.7 |
| 2 | 33 | 6.48 | 6.78 | 1.2 |

Difference = μ(1) – μ(2)

Estimate for difference: -8.19

95% CI for difference: (-12.18, -4.20)

T-Test of difference = 0 (vs not =): T-Value = -4.11 p-value = 0.000 DF = 55

Both use Pooled St. Dev = 7.42

## Sleep

### Two-Sample T-Test and CI: Sleep Q5_s-3, group

Two-sample T for Sleep Q5_s-3

| group | N | Mean | St. Dev | SE Mean |
|---|---|---|---|---|
| 1 | 24 | 0.71 | 4.88 | 1.0 |
| 2 | 34 | 1.16 | 4.19 | 0.72 |

Difference = μ(1) – μ(2)

Estimate for difference: -0.45

95% CI for difference: (-2.85, 1.94)

T-Test of difference = 0 (vs not =): T-Value = -0.38 p-value = 0.706 DF = 56

Both use Pooled St. Dev = 4.49

### Two-Sample T-Test and CI: Sleep Q5_s-6, group

Two-sample T for Sleep Q5_s-6

| group | N | Mean | St. Dev | SE Mean |
|---|---|---|---|---|
| 1 | 24 | 1.10 | 4.54 | 0.93 |
| 2 | 33 | 1.98 | 5.64 | 0.98 |

Difference = μ(1) – μ(2)

Estimate for difference: -0.87

95% CI for difference: (-3.67, 1.93)

T-Test of difference = 0 (vs not =): T-Value = -0.62 p-value = 0.535 DF = 55

Both use Pooled St. Dev = 5.21

**Two-Sample T-Test and CI: Sleep Q5_s-9, group**

Two-sample T for Sleep Q5_s-9

| group | N | Mean | St. Dev | SE Mean |
|---|---|---|---|---|
| 1 | 24 | -1.48 | 5.97 | 1.2 |
| 2 | 33 | 2.73 | 4.88 | 0.85 |

Difference = μ(1) – μ(2)

Estimate for difference: -4.21

95% CI for difference: (-7.09, -1.32)

T-Test of difference = 0 (vs not =): T-Value = -2.92 p-value = 0.005 DF = 55

Both use Pooled St. Dev = 5.37

**Two-Sample T-Test and CI: Sleep Q5_s-12, group**

Two-sample T for Sleep Q5_s-12

| group | N | Mean | St. Dev | SE Mean |
|---|---|---|---|---|
| 1 | 24 | 0.54 | 5.73 | 1.2 |
| 2 | 33 | 4.45 | 4.66 | 0.81 |

Difference = μ(1) – μ(2)

Estimate for difference: -3.91

95% CI for difference: (-6.67, -1.15)

T-Test of difference = 0 (vs not =): T-Value = -2.84 p-value = 0.006 DF = 55

Both use Pooled St. Dev = 5.13

## Cognitive Function

### Two-Sample T-Test and CI: CFQ Q6_s-3, group

Two-sample T for CFQ Q6_s-3

| group | N | Mean | St. Dev | SE Mean |
|---|---|---|---|---|
| 1 | 24 | 3.08 | 7.29 | 1.5 |
| 2 | 34 | 3.50 | 9.11 | 1.6 |

Difference = μ(1) – μ(2)

Estimate for difference: -0.42

95% CI for difference: (-4.91, 4.07)

T-Test of difference = 0 (vs not =): T-Value = -0.19 p-value = 0.853 DF = 56

Both use Pooled St. Dev = 8.41

### Two-Sample T-Test and CI: CFQ Q6_s-6, group

Two-sample T for CFQ Q6_s-6

| group | N | Mean | St. Dev | SE Mean |
|---|---|---|---|---|
| 1 | 24 | 0.33 | 8.13 | 1.7 |
| 2 | 33 | 7.73 | 9.91 | 1.7 |

Difference = μ(1) – μ(2)

Estimate for difference: -7.39

95% CI for difference: (-12.34, -2.44)

T-Test of difference = 0 (vs not =): T-Value = -2.99 p-value = 0.004 DF = 55

Both use Pooled St. Dev = 9.21

**Two-Sample T-Test and CI: CFQ Q6_s-9, group**

Two-sample T for CFQ Q6_s-9

| group | N | Mean | St. Dev | SE Mean |
|---|---|---|---|---|
| 1 | 24 | 1.21 | 7.56 | 1.5 |
| 2 | 33 | 10.3 | 12.4 | 2.2 |

Difference = μ(1) – μ(2)

Estimate for difference: -9.13

95% CI for difference: (-14.85, -3.40)

T-Test of difference = 0 (vs not =): T-Value = -3.19 p-value = 0.002 DF = 55

Both use Pooled St. Dev = 10.7

**Two-Sample T-Test and CI: CFQ Q6_s-12, group**

Two-sample T for CFQ Q6_s-12

| group | N | Mean | St. Dev | SE Mean |
|---|---|---|---|---|
| 1 | 24 | -0.33 | 7.48 | 1.5 |
| 2 | 33 | 13.1 | 10.7 | 1.9 |

Difference = μ(1) – μ(2)

Estimate for difference: -13.42

95% CI for difference: (-18.51, -8.33)

T-Test of difference = 0 (vs not =): T-Value = -5.29 p-value = 0.000 DF = 55

Both use Pooled St. Dev = 9.47

Two-Sample T-Test and CI: Nott. Q7_s-3, group

Two-sample T for Nott. Q7_s-3

| group | N | Mean | St. Dev | SE Mean |
|---|---|---|---|---|
| 1 | 24 | 0.71 | 2.99 | 0.61 |
| 2 | 34 | 2.82 | 6.09 | 1.0 |

Difference = μ(1) – μ(2)

Estimate for difference: -2.12

95% CI for difference: (-4.81, 0.58)

T-Test of difference = 0 (vs not =): T-Value = -1.57 p-value = 0.122 DF = 56

Both use Pooled St. Dev = 5.05

Two-Sample T-Test and CI: Nott. Q7_s-6, group

Two-sample T for Nott. Q7_s-6

| group | N | Mean | St. Dev | SE Mean |
|---|---|---|---|---|
| 1 | 24 | 0.50 | 3.62 | 0.74 |
| 2 | 33 | 5.52 | 6.45 | 1.1 |

Difference = μ(1) – μ(2)

Estimate for difference: -5.02

95% CI for difference: (-7.95, -2.08)

T-Test of difference = 0 (vs not =): T-Value = -3.43 p-value = 0.001 DF = 55

Both use Pooled St. Dev = 5.45

Two-Sample T-Test and CI: Nott. Q7_s-9, group

Two-sample T for Nott. Q7_s-9

| group | N | Mean | St. Dev | SE Mean |
|---|---|---|---|---|
| 1 | 24 | 0.46 | 3.96 | 0.81 |
| 2 | 33 | 6.12 | 6.20 | 1.1 |

Difference = μ(1) – μ(2)

Estimate for difference: -5.66

95% CI for difference: (-8.55, -2.77)

T-Test of difference = 0 (vs not =): T-Value = -3.92 p-value = 0.000 DF = 55

Both use Pooled St. Dev = 5.38

Two-Sample T-Test and CI: Nott. Q7_s-12, group

Two-sample T for Nott. Q7_s-12

| group | N | Mean | St. Dev | SE Mean |
|---|---|---|---|---|
| 1 | 24 | -0.92 | 4.87 | 0.99 |
| 2 | 33 | 6.85 | 6.50 | 1.1 |

Difference = μ(1) – μ(2)

Estimate for difference: -7.77

95% CI for difference: (-10.92, -4.61)

T-Test of difference = 0 (vs not =): T-Value = -4.93 p-value = 0.000 DF = 55

Both use Pooled St. Dev = 5.87

Two-Sample T-Test and CI: PFRS Q8_s-3, group

Two-sample T for PFRS Q8_s-3

| group | N | Mean | St. Dev | SE Mean |
|---|---|---|---|---|
| 1 | 24 | 6.2 | 30.6 | 6.3 |
| 2 | 34 | 34.1 | 56.3 | 9.7 |

Difference = μ(1) – μ(2)

Estimate for difference: -27.9

95% CI for difference: (-53.3, -2.6)

T-Test of difference = 0 (vs not =): T-Value = -2.21 p-value = 0.032 DF = 56

Both use Pooled St. Dev = 47.5

Two-Sample T-Test and CI: PFRS Q8_s-6, group

Two-sample T for PFRS Q8_s-6

| group | N | Mean | St. Dev | SE Mean |
|---|---|---|---|---|
| 1 | 24 | 9.3 | 28.8 | 5.9 |
| 2 | 33 | 58.6 | 56.4 | 9.8 |

Difference = μ(1) – μ(2)

Estimate for difference: -49.4

95% CI for difference: (-74.5, -24.2)

T-Test of difference = 0 (vs not =): T-Value = -3.93 p-value = 0.000 DF = 55

Both use Pooled St. Dev = 46.9

Two-Sample T-Test and CI: PFRS Q8_s-9, group

Two-sample T for PFRS Q8_s-9

| group | N | Mean | St. Dev | SE Mean |
|---|---|---|---|---|
| 1 | 24 | 7.6 | 41.4 | 8.4 |
| 2 | 33 | 66.7 | 59.5 | 10 |

Difference = μ(1) – μ(2)

Estimate for difference: -59.1

95% CI for difference: (-87.4, -30.8)

T-Test of difference = 0 (vs not =): T-Value = -4.18 p-value = 0.000 DF = 55

Both use Pooled St. Dev = 52.7

Two-Sample T-Test and CI: PFRS Q8_s-12, group

Two-sample T for PFRS Q8_s-12

| group | N | Mean | St. Dev | SE Mean |
|---|---|---|---|---|
| 1 | 24 | -8.0 | 42.1 | 8.6 |
| 2 | 33 | 70.2 | 56.2 | 9.8 |

Difference = μ(1) – μ(2)

Estimate for difference: -78.2

95% CI for difference: (-105.5, -50.9)

T-Test of difference = 0 (vs not =): T-Value = -5.74 p-value = 0.000 DF = 55

Both use Pooled St. Dev = 50.8

## Follow Up Study

For each questionnaire a one-sample t test of the hypothesis that there is no change from month 12 until follow up was carried out for patients only. There are no significant changes for these data, as the p-values all exceed 0.05.

**One-Sample T: Health Q1_12-f, Back Q2_12-f, BDI Q3_12-f, BAI Q4_12-f, Sleep Q5_12-f CFQ Q6_12-f, Nott. Q7_12-f, PFRS Q8_12-f.**

Test of $\mu = 0$ vs $\mu$ not $= 0$

| Variable | | N | Mean | St. Dev | SE Mean |
|---|---|---|---|---|---|
| Health | Q1_12-f | 16 | -0.84 | 7.96 | 1.99 |
| Back | Q2_12-f | 16 | 0.94 | 5.82 | 1.46 |
| BDI | Q3_12-f | 16 | 1.75 | 6.50 | 1.62 |
| BAI | Q4_12-f | 16 | 3.88 | 7.92 | 1.98 |
| Sleep | Q5_12-f | 16 | -0.156 | 3.249 | 0.812 |
| CFQ | Q6_12-f | 16 | 0.63 | 11.96 | 2.99 |
| Nott. | Q7_12-f | 16 | 0.563 | 3.633 | 0.908 |
| PFRS | Q8_12-f | 16 | -10.69 | 31.42 | 7.85 |

| Variable | | 95.0% CI | T | p |
|---|---|---|---|---|
| Health | Q1_12-f | (-5.09, 3.40) | -0.42 | 0.678 |
| Back | Q2_12-f | (-2.7, 4.04) | 0.64 | 0.529 |
| BDI | Q3_12-f | (-1.71, 5.21) | 1.08 | 0.298 |
| BAI | Q4_12-f | (-0.34, 8.09) | 1.96 | 0.069 |
| Sleep | Q5_12-f | (-1.89,1.58) | -0.19 | 0.850 |
| CFQ | Q6_12-f | (-5.75, 7.00) | 0.21 | 0.837 |
| Nott. | Q7_12-f | (-1.373, 2.498) | 0.62 | 0.545 |
| PFRS | Q8_12-f | (-27.43, 6.05) | -1.36 | 0.194 |

## APPENDIX A10: Statistical analysis of questionnaires (phase 2)

Statistical software package used: SPSS for Windows.

1 = treated group; 2 = non-treated cfs/me group; 3 = healthy group

### Kruskal-Wallis Test: HEALTH versus Group

| Group | N | Median | Ave Rank | Z |
|---|---|---|---|---|
| 1 | 9 | 8.96E+00 | 20.6 | 3.03 |
| 2 | 9 | 0.00E+00 | 11.0 | -1.39 |
| 3 | 9 | 0.00E+00 | 10.4 | -1.65 |
| Overall | 27 | | 14.0 | |

H = 9.36 DF = 2 p = 0.009 (adjusted for ties)

### Kruskal-Wallis Test: Back Pain versus Group

| Group | N | Median | Ave Rank | Z |
|---|---|---|---|---|
| 1 | 9 | 1.95E+01 | 21.5 | 3.47 |
| 2 | 9 | 0.00E+00 | 10.4 | -1.65 |
| 3 | 9 | 0.00E+00 | 10.1 | -1.83 |
| Overall | 27 | | 14.0 | |

H = 12.18 DF = 2 p = 0.002 (adjusted for ties)

### Kruskal-Wallis Test: Depression versus Group

| Group | N | Median | Ave Rank | Z |
|---|---|---|---|---|
| 1 | 9 | 7.95E+00 | 18.9 | 2.29 |
| 2 | 9 | -3.2E+00 | 10.3 | -1.72 |
| 3 | 9 | 0.00E+00 | 12.8 | -0.57 |
| Overall | 27 | | 14.0 | |

H = 5.74 DF = 2 p = 0.057 (adjusted for ties)

### Kruskal-Wallis Test: Anxiety versus Group

| Group | N | Median | Ave Rank | Z |
|---|---|---|---|---|
| 1 | 9 | 7.95E+00 | 16.3 | 1.08 |
| 2 | 9 | 4.77E+00 | 13.6 | -0.18 |
| 3 | 9 | 0.00E+00 | 12.1 | -0.90 |
| Overall | 27 | | 14.0 | |

H = 1.36 DF = 2 p = 0.507 (adjusted for ties)

### Kruskal-Wallis Test: Sleep versus Group

| Group | N | Median | Ave Rank | Z |
|---|---|---|---|---|
| 1 | 9 | 9.080 | 18.9 | 2.26 |
| 2 | 9 | -4.540 | 10.7 | -1.52 |
| 3 | 9 | -2.270 | 12.4 | -0.75 |
| Overall | 27 | | 14.0 | |

H = 5.33 DF = 2 p = 0.069 (adjusted for ties)

## Kruskal-Wallis Test: Cognition versus Group

| Group | N | Median | Ave Rank | Z |
|---|---|---|---|---|
| 1 | 9 | 9.000 | 20.1 | 2.80 |
| 2 | 9 | -3.000 | 10.4 | -1.65 |
| 3 | 9 | -9.000 | 11.5 | -1.16 |
| Overall | 27 | | 14.0 | |

H = 7.97 DF = 2 p = 0.019 (adjusted for ties)

## Kruskal-Wallis Test: Nott. Health versus Group

| Group | N | Median | Ave Rank | Z |
|---|---|---|---|---|
| 1 | 9 | 2.63E+00 | 16.0 | 0.93 |
| 2 | 9 | 0.00E+00 | 15.4 | 0.67 |
| 3 | 9 | 0.00E+00 | 10.6 | -1.59 |
| Overall | 27 | | 14.0 | |

H = 2.67 DF = 2 p = 0.263 (adjusted for ties)

## Kruskal-Wallis Test: PFRS. versus Group

| Group | N | Median | Ave Rank | Z |
|---|---|---|---|---|
| 1 | 9 | 1.98E+01 | 20.4 | 2.98 |
| 2 | 9 | -1.6E+00 | 8.8 | -2.42 |
| 3 | 9 | 0.00E+00 | 12.8 | -0.57 |
| Overall | 27 | | 14.0 | |

H = 10.06 DF = 2 p = 0.007 (adjusted for ties)

NB A -ve score indicates mean worsening of symptoms.

A p-value less than 0.05 indicates significance at the 5% level. Hence significant difference were found for questionnaires 1,2,6 and 8, but not for questionnaires 3,4,5,and 7. For all eight questionnaires the estimated median increase is greatest in the treated patients (group1).

## APPENDIX A11: Detailed data from MRI scans

The following charts contains the values for CSF proportional volume, change in proportional volume, ventricle proportional volume and change in ventricle proportional volume Data was arranged in patient groups matched for age and sex.

1a = first scan at start

1b = second scan at start

2a = first scan 1 year later

Since there was no change between the 1a and 1b data of 2b (second scan at end on year) was not calculated.

Data is in mm3

The proportion of CSF volume expressed as a percentage of the total volume of the bounding box is shown in the following table

| treated cfs | untreated cfs | normals |
|---|---|---|
| 2.342 | 3.009 | 4.218 |
| 2.460 | 4.986 | 3.002 |
| 3.516 | 4.220 | 3.923 |
| 3.122 | 4.138 | 2.201 |
| 5.153 | 3.245 | 2.959 |
| 4.054 | 3.473 | 4.145 |
| 6.575 | 6.867 | 4.121 |
| 5.802 | 3.516 | 5.697 |
| 5.322 | 6.262 | 3.989 |

**CSF proportion of bounding box at start/%**

| Source | SS | Df | MS | Chi-sq | Prob>Chi-sq | |
|---|---|---|---|---|---|---|
| Columns | 16.2222 | 2 | 8.1111 | 2.163 | 0.33909 | |
| Interaction | 33.7778 | 4 | 8.4444 | | | |
| Error | 130 | 18 | 7.2222 | | | |
| Total | 180 | 26 | | | | |

**Friedman's ANOVA Table for statistical analysis of above data**

(statistical software package used: MATLAB)

The proportion of CSF volume change expressed as a percentage of the total volume of the bounding box is shown below.

| treated cfs | Untreated cfs | Normals |
|---|---|---|
| 1.142 | 1.046 | 1.025 |
| 1.116 | 1.054 | 1.199 |
| 1.011 | 1.256 | 1.083 |
| 1.075 | 0.755 | 1.181 |
| 0.970 | 0.980 | 1.015 |
| 0.995 | 1.010 | 1.059 |
| 1.031 | 0.979 | 0.993 |
| 0.971 | 1.127 | 0.975 |
| 1.052 | 1.015 | 1.075 |

**Proportional change in CFS proportion of bounding box after 1 year/ %**

| Source | SS | Df | MS | Chi-sq | Prob>Chi-sq | |
|---|---|---|---|---|---|---|
| Columns | 6 | 2 | 3 | 0.8 | 0.67032 | |
| Interaction | 25.3333 | 4 | 6.3333 | | | |
| Error | 148.6667 | 18 | 8.2593 | | | |
| Total | 180 | 26 | | | | |

**Friedman's ANOVA Table for statistical analysis of above data**

The proportion of CSF volume in just the ventricles expressed as a percentage of the total volume of the bounding box is shown below.

| Treated cfs | untreated cfs | Normals |
|---|---|---|
| 0.168 | 0.092 | 0.144 |
| 0.113 | 0.258 | 0.212 |
| 0.214 | 0.203 | 0.080 |
| 0.096 | 0.132 | 0.075 |
| 0.091 | 0.177 | 0.194 |
| 0.219 | 0.081 | 0.181 |
| 0.194 | 0.280 | 0.191 |
| 0.206 | 0.218 | 0.176 |
| 0.138 | 0.215 | 0.155 |

**Ventricular proportion of CSF bounding box at start/%**

| Source | SS | Df | MS | Chi-sq | Prob>Chi-sq | |
|---|---|---|---|---|---|---|
| Columns | 16.2222 | 2 | 8.1111 | 2.163 | 0.33909 | |
| Interaction | 32.4444 | 4 | 8.1111 | | | |
| Error | 131.3333 | 18 | 7.2963 | | | |
| Total | 180 | 26 | | | | |

**Friedman's ANOVA Table for statistical analysis of above data**

| treated cfs | Untreated cfs | Normals |
|---|---|---|
| 0.985 | 1.043 | 0.952 |
| 1.058 | 0.959 | 1.026 |
| 0.992 | 1.100 | 0.970 |
| 1.036 | 0.777 | 1.134 |
| 1.001 | 1.007 | 0.943 |
| 0.961 | 1.050 | 1.030 |
| 0.998 | 0.948 | 0.977 |
| 1.004 | 1.067 | 1.022 |
| 1.050 | 1.039 | 1.030 |

**Proprtional change in Ventricular volume over 1 year/%**

| Source | SS | Df | MS | Chi-sq | Prob>Chi-sq |
|---|---|---|---|---|---|
| Columns | 4.667 | 2.000 | 2.3333 | 0.62222 | 0.73263 |
| Interaction | 12.667 | 4.000 | 3.1667 | | |
| Error | 162.667 | 18.000 | 9.037 | | |
| Total | 180.000 | 26.000 | | | |

**Raw measurements of ventricular volume**

(statistical software package used: MATLAB)

| | 1b space % of 1a | 1a csf% of box | 1b csf% of box | 2a csf% of box | Mean 1a1b | 2a as a % of μ (1a1b) |
|---|---|---|---|---|---|---|
| RV06 | 99.149 | 2.412 | 2.273 | 2.674 | 2.342 | 114.160 |
| RV08 | 100.704 | 2.505 | 2.416 | 2.745 | 2.460 | 111.577 |
| RV03 | 99.908 | 3.451 | 3.581 | 3.555 | 3.516 | 101.093 |
| RV10 | 101.613 | 3.072 | 3.172 | 3.355 | 3.122 | 107.472 |
| RV01 | 100.000 | 5.158 | 5.148 | 4.999 | 5.153 | 97.017 |
| RV07 | 104.288 | 4.097 | 4.011 | 4.034 | 4.054 | 99.490 |
| RV04 | 98.588 | 6.499 | 6.652 | 6.780 | 6.575 | 103.106 |
| RV09 | 100.137 | 5.804 | 5.800 | 5.636 | 5.802 | 97.133 |
| RV05 | 104.469 | 5.404 | 5.240 | 5.597 | 5.322 | 105.160 |
| | | | | | | |
| CP09 | 99.080 | 2.939 | 3.078 | 3.146 | 3.009 | 104.562 |
| CP05 | 103.865 | 5.126 | 4.846 | 5.257 | 4.986 | 105.430 |
| CP08 | 99.947 | 4.326 | 4.113 | 5.300 | 4.220 | 125.602 |
| CP06 | 95.421 | 4.227 | 4.048 | 3.125 | 4.138 | 75.518 |
| CP03 | 103.925 | 3.316 | 3.174 | 3.181 | 3.245 | 98.024 |
| CP02 | 94.637 | 3.366 | 3.580 | 3.508 | 3.473 | 101.001 |
| CP01 | 103.042 | 6.971 | 6.763 | 6.723 | 6.867 | 97.899 |
| CP04 | 107.169 | 3.503 | 3.529 | 3.963 | 3.516 | 112.702 |
| CP07 | 99.548 | 6.141 | 6.382 | 6.355 | 6.262 | 101.492 |
| | | | | | | |
| NC07 | 101.527 | 4.264 | 4.171 | 4.324 | 4.218 | 102.520 |
| NC08 | 97.761 | 3.125 | 2.878 | 3.600 | 3.002 | 119.918 |
| NC05 | 100.000 | 3.779 | 4.067 | 4.250 | 3.923 | 108.344 |
| NC09 | 96.048 | 2.075 | 2.327 | 2.600 | 2.201 | 118.128 |
| NC03 | 98.216 | 3.045 | 2.874 | 3.003 | 2.959 | 101.488 |
| NC04 | 98.469 | 4.208 | 4.081 | 4.391 | 4.145 | 105.938 |
| NC06 | 99.048 | 4.172 | 4.070 | 4.093 | 4.121 | 99.319 |
| NC01 | 98.507 | 5.464 | 5.930 | 5.555 | 5.697 | 97.511 |
| NC02 | 102.381 | 4.031 | 3.946 | 4.289 | 3.989 | 107.523 |

## Change in CSF Proportions expressed as a percentage

No significant difference was seen between the first scan 1a and 90 minutes later (1b). Thus only csf proportions of 2a, at the end of the year, were analysed. (Final column = 100 x (2a)/μ (1a+1b))

| | 1a total | 1b total | 2a total | 1b as % of 1a | 2a as % of 1a |
|---|---|---|---|---|---|
| RV05 | 132014.4 | 133719.2252 | 133535.2 | 101.291362 | 101.152 |
| RV04 | 168218.6 | 169768.3682 | 157047 | 100.921305 | 93.35893 |
| RV09 | 153108 | 153201.5835 | 134687.9 | 100.061153 | 87.96921 |
| RV01 | 145533.3 | 145262.056 | 135743.7 | 99.8136394 | 93.27328 |
| RV03 | 98974.51 | 102597.1788 | 98041.39 | 103.660206 | 99.05722 |
| RV07 | 84722.75 | 86508.25214 | 82672.48 | 102.107471 | 97.58003 |
| RV06 | 54711.39 | 51114.5504 | 57297.63 | 93.4257905 | 104.7271 |
| RV10 | 68582.16 | 71962.67499 | 73732.04 | 104.929148 | 107.5091 |
| RV08 | 68210.85 | 66257.44852 | 71940.07 | 97.1362285 | 105.4672 |
| CP06 | 118666.7 | 108438.0102 | 82543.33 | 91.380294 | 69.55895 |
| CP09 | 79385.6 | 82398.03809 | 79960.32 | 103.79469 | 100.724 |
| CP05 | 149643.5 | 146941.0146 | 151238.5 | 98.1940593 | 101.0659 |
| CP08 | 118718.4 | 112809.7574 | 145439.6 | 95.0229814 | 122.5081 |
| CP03 | 79886.06 | 79479.23599 | 71843.21 | 99.4907459 | 89.9321 |
| CP01 | 188340.2 | 188291.7847 | 182974 | 99.9742864 | 97.15079 |
| CP02 | 98955.13 | 99578.28473 | 102358.3 | 100.629731 | 103.4391 |
| CP04 | 100701.9 | 108722.144 | 111699.1 | 107.964348 | 110.9205 |
| CP07 | 165645.2 | 171353.694 | 168254.1 | 103.446194 | 101.575 |
| NC01 | 150909.2 | 161338.0684 | 139689.2 | 106.910718 | 92.5651 |
| NC02 | 114010.9 | 114256.2428 | 125579.5 | 100.215231 | 110.147 |
| NC04 | 123261.3 | 117707.7917 | 121091.5 | 95.4945518 | 98.23973 |
| NC06 | 94338 | 91147.9859 | 97234.2 | 96.6185235 | 103.07 |
| NC05 | 101841.6 | 109610.0523 | 120875.2 | 107.627926 | 118.6894 |
| NC09 | 42445.32 | 45728.97284 | 52912.97 | 107.736193 | 124.6615 |
| NC07 | 114772.8 | 113994.7105 | 109342.1 | 99.3220227 | 95.26824 |
| NC03 | 74468.19 | 69027.7284 | 68840.46 | 92.6942432 | 92.44277 |
| NC08 | 88054.83 | 79272.59326 | 99746.18 | 90.0264002 | 113.2774 |

**Raw measurements of CSF and bounding box volumes in mm3**

| | 1b space % of 1a | 1a csf% of box | 1b csf% of box | 2a csf% of box | mean 1a1b | dif 1 year |
|---|---|---|---|---|---|---|
| RV05 | 104.4691648 | 5.40415148 | 5.239764918 | 5.596557359 | 5.321958199 | 105.1597391 |
| RV04 | 98.5880357 | 6.498528023 | 6.6523278 | 6.779661154 | 6.575427911 | 103.1060069 |
| RV09 | 100.136842 | 5.804161396 | 5.799774318 | 5.635623642 | 5.801967857 | 97.13296903 |
| RV01 | 100 | 5.157585959 | 5.147974251 | 4.999084254 | 5.152780105 | 97.01722472 |
| RV03 | 99.90801183 | 3.451385738 | 3.581007681 | 3.554629873 | 3.516196709 | 101.0930322 |
| RV07 | 104.2878758 | 4.097068004 | 4.011408304 | 4.033553762 | 4.054238154 | 99.48980817 |
| RV06 | 99.14941582 | 2.411838758 | 2.272609886 | 2.673879008 | 2.342224322 | 114.1598174 |
| RV10 | 101.6129023 | 3.071515031 | 3.171757199 | 3.35488068 | 3.121636115 | 107.4718691 |
| RV08 | 100.7042191 | 2.504623745 | 2.415883927 | 2.745088052 | 2.460253836 | 111.577432 |
| CP06 | 95.42143531 | 4.227397961 | 4.048365729 | 3.124854761 | 4.137881845 | 75.51822112 |
| CP09 | 99.07994959 | 2.93858916 | 3.07842254 | 3.145768607 | 3.00850585 | 104.5624893 |
| CP05 | 103.8647335 | 5.125882367 | 4.846025982 | 5.256702132 | 4.985954174 | 105.4302135 |
| CP08 | 99.94704448 | 4.326426424 | 4.113277583 | 5.300222311 | 4.219852004 | 125.60209 |
| CP03 | 103.9253684 | 3.315857414 | 3.174365724 | 3.180981731 | 3.245111569 | 98.02380175 |
| CP01 | 103.0416943 | 6.97054186 | 6.763038527 | 6.722540064 | 6.866790194 | 97.89930774 |
| CP02 | 94.63727948 | 3.366447179 | 3.579611278 | 3.5077897 | 3.473029229 | 101.000869 |
| CP04 | 107.1688043 | 3.503303361 | 3.52930935 | 3.962953538 | 3.516306355 | 112.7021692 |
| CP07 | 99.54810563 | 6.141313705 | 6.381794271 | 6.355000001 | 6.261553988 | 101.4923773 |
| NC01 | 98.50746344 | 5.463635705 | 5.929715345 | 5.554870537 | 5.696675525 | 97.51074136 |
| NC02 | 102.3809524 | 4.031156961 | 3.945883658 | 4.288581044 | 3.98852031 | 107.5231091 |
| NC04 | 98.46856059 | 4.208483905 | 4.081376654 | 4.391054742 | 4.14493028 | 105.9379639 |
| NC06 | 99.04777904 | 4.171842265 | 4.069523253 | 4.092601366 | 4.120682759 | 99.31852572 |
| NC05 | 100 | 3.778534655 | 4.066758474 | 4.249954621 | 3.922646565 | 108.3440619 |
| NC09 | 96.04796644 | 2.074646793 | 2.327113793 | 2.599850443 | 2.200880293 | 118.1277533 |
| NC07 | 101.5267168 | 4.2638456 | 4.171254456 | 4.323838988 | 4.217550028 | 102.5201588 |
| NC03 | 98.21574652 | 3.04468796 | 2.873521366 | 3.003143866 | 2.959104663 | 101.4882611 |
| NC08 | 97.76119558 | 3.125343736 | 2.878068791 | 3.599575745 | 3.001706264 | 119.9176544 |

**Raw measurements of CSF and bounding box volumes in mm3 cont.**

| | 1a csf space | 1b csf space | 2a csf space |
|---|---|---|---|
| RV05 | 2442833.832 | 2552008.102 | 2386023.743 |
| RV04 | 2588564.073 | 2552014.472 | 2316443.853 |
| RV09 | 2637899.641 | 2641509.395 | 2389937.02 |
| RV01 | 2821732.374 | 2821732.374 | 2715370.545 |
| RV03 | 2867674.467 | 2865036.546 | 2758132.263 |
| RV07 | 2067887.208 | 2156555.643 | 2049618.901 |
| RV06 | 2268451.476 | 2249156.387 | 2142865.544 |
| RV10 | 2232844.65 | 2268858.253 | 2197754.349 |
| RV08 | 2723397.141 | 2742575.824 | 2620683.627 |
| | | | |
| CP06 | 2807086.885 | 2678562.597 | 2641509.373 |
| CP09 | 2701486.888 | 2676631.846 | 2541837.35 |
| CP05 | 2919370.298 | 3032196.179 | 2877060.418 |
| CP08 | 2744028.958 | 2742575.844 | 2744028.958 |
| CP03 | 2409212.733 | 2503783.209 | 2258523.184 |
| CP01 | 2701945.091 | 2784130.002 | 2721798.776 |
| CP02 | 2939453.039 | 2781818.387 | 2918027.012 |
| CP04 | 2874484.005 | 3080550.138 | 2818581.168 |
| CP07 | 2697228.075 | 2685039.454 | 2647585.823 |
| | | | |
| NC01 | 2762064.851 | 2720840.023 | 2514715.885 |
| NC02 | 2828241.543 | 2895580.628 | 2928229.981 |
| NC04 | 2928875.741 | 2884021.783 | 2757686.754 |
| NC06 | 2261303.216 | 2239770.613 | 2375853.243 |
| NC05 | 2695268.308 | 2695268.308 | 2844152.95 |
| NC09 | 2045905.886 | 1965050.999 | 2035231.355 |
| NC07 | 2691768.302 | 2732863.979 | 2528819.117 |
| NC03 | 2445839.92 | 2402199.936 | 2292279.845 |
| NC08 | 2817444.639 | 2754367.564 | 2771053.835 |

**Raw measurements of CSF space**

Numbers of DWMH in regions of brain reported by radiologist from FLAIR scan

| code no. | Scan No | T2 frontal | T2 Parietal | T2 Occipital | T2 Temporal | T2 frontal | T2 Parietal | T2 Occipital | T2 Temporal | PVH |
|---|---|---|---|---|---|---|---|---|---|---|
| rv01 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| rv01 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| rv01 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| rv01 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| rv01 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| rv01 | 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| rv03 | 1 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| rv03 | 2 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| rv03 | 3 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| rv03 | 4 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| rv03 | 5 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| rv03 | 6 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| rv04 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| rv04 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| rv04 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| rv04 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| rv04 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| rv04 | 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| rv05 | 1 | 0 | 3 | 0 | 3 | 0 | 0 | 0 | 0 | 0 |
| rv05 | 2 | 0 | 3 | 0 | 3 | 0 | 0 | 0 | 0 | 0 |
| rv05 | 3 | 0 | 3 | 0 | 3 | 0 | 0 | 0 | 0 | 0 |
| rv05 | 4 | 0 | 3 | 0 | 3 | 0 | 0 | 0 | 0 | 0 |
| rv05 | 5 | 0 | 3 | 0 | 3 | 0 | 0 | 0 | 0 | 0 |
| rv05 | 6 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| rv06 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| rv06 | 2 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| rv06 | 3 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| rv06 | 4 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| rv06 | 5 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| rv06 | 6 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 |
| rv07 | 1 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| rv07 | 2 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| rv07 | 3 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| rv07 | 4 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| rv07 | 5 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| rv07 | 6 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| rv08 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| rv08 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| rv08 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| rv08 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| rv08 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| rv08 | 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

Numbers of DWMH in regions of brain reported by radiologist from FLAIR scan cont.

| code no. | Scan No | T2 frontal | T2 Parietal | T2 Occipital | T2 Temporal | T2 frontal | T2 Parietal | T2 Occipital | T2 Temporal | PVH |
|---|---|---|---|---|---|---|---|---|---|---|
| rv09 | 1 | 0 | 1 | 0 | 3 | 0 | 0 | 0 | 0 | 0 |
| rv09 | 2 | 0 | 1 | 0 | 3 | 0 | 0 | 0 | 0 | 0 |
| rv09 | 3 | 0 | 1 | 0 | 3 | 0 | 0 | 0 | 0 | 0 |
| rv09 | 4 | 0 | 1 | 0 | 3 | 0 | 0 | 0 | 0 | 0 |
| rv09 | 5 | 0 | 1 | 0 | 3 | 0 | 0 | 0 | 0 | 0 |
| rv09 | 6 | 0 | 1 | 0 | 3 | 0 | 0 | 0 | 0 | 0 |
| rv10 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| rv10 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| rv10 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| rv10 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| rv10 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| rv10 | 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

**DWMH:complete findings of scans of treated group**

| code number | Scan No | T2 frontal | T2 Parietal | T2 Occipital | T2 Temporal | T2 frontal | T2 Parietal | T2 Occipital | T2 Temporal | PVH |
|---|---|---|---|---|---|---|---|---|---|---|
| cp01 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| cp01 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| cp01 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 |
| cp01 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| cp02 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| cp02 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| cp02 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| cp02 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| cp02 | 5 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| cp02 | 6 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| cp03 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| cp03 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| cp03 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| cp03 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| cp04 | 1 | 3 | 2 | 3 | 1 | 2 | 3 | 3 | 1 | 2 |
| cp04 | 2 | 3 | 2 | 3 | 1 | 2 | 3 | 3 | 1 | 2 |
| cp04 | 3 | 3 | 2 | 3 | 1 | 2 | 3 | 3 | 1 | 2 |
| cp04 | 4 | 3 | 2 | 3 | 1 | 2 | 3 | 3 | 1 | 2 |
| cp05 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| cp05 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| cp05 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| cp05 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| cp06 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| cp06 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| cp06 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| cp06 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| cp07 | 1 | 3 | 1 | 3 | 1 | 2 | 1 | 0 | 0 | 1 |
| cp07 | 2 | 3 | 1 | 3 | 1 | 2 | 1 | 0 | 0 | 1 |
| cp07 | 3 | 3 | 1 | 3 | 1 | 2 | 1 | 0 | 0 | 1 |
| cp07 | 4 | 3 | 1 | 3 | 1 | 2 | 1 | 0 | 0 | 1 |
| cp08 | 1 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| cp08 | 2 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| cp08 | 3 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| cp08 | 4 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| cp09 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| cp09 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| cp09 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| cp09 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |

**DWMH:complete findings of scans of untreated cfs/me group**

| code number | Scan No | T2 frontal | T2 Parietal | T2 Occipital | T2 Temporal | T2 frontal | T2 Parietal | T2 Occipital | T2 Temporal | PVH |
|---|---|---|---|---|---|---|---|---|---|---|
| nc01 | 1 | 0 | 2 | 0 | 2 | 3 | 3 | 1 | 2 | 0 |
| nc01 | 2 | 0 | 2 | 0 | 2 | 3 | 3 | 1 | 2 | 0 |
| nc01 | 3 | 0 | 2 | 0 | 2 | 3 | 3 | 1 | 2 | 0 |
| nc01 | 4 | 0 | 2 | 0 | 2 | 3 | 3 | 1 | 2 | 0 |
| nc02 | 1 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| nc02 | 2 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| nc02 | 3 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| nc02 | 4 | 1 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 |
| nc05 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| nc05 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| nc05 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| nc05 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| nc06 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| nc06 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| nc06 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| nc06 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| nc07 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| nc07 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| nc07 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| nc07 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| nc09 | 1 | 1 | 3 | 1 | 0 | 3 | 1 | 0 | 0 | 0 |
| nc09 | 2 | 1 | 3 | 1 | 0 | 3 | 1 | 0 | 0 | 0 |
| nc09 | 3 | 1 | 3 | 1 | 0 | 3 | 1 | 0 | 0 | 0 |
| nc09 | 4 | 1 | 3 | 1 | 0 | 3 | 1 | 0 | 0 | 0 |
| nco3 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| nco3 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| nco3 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| nco3 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| nco4 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| nco4 | 2 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| nco4 | 3 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| nco4 | 4 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| nco8 | 1 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| nco8 | 2 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| nco8 | 3 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |
| nco8 | 3 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 1 |

**DWMH:complete findings of scans of healthy group**

| | age_ y | Sex | No +ve div | no - ve div | Sum +ve ml/min | Sum –ve ml/min | net flow ml/min | max +ve ml/sec | max – ve ml/sec | 1st 0 cross | 2nd 0 cross | Max dif ml/sec |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| RV06 | 20 | F | 64 | 86 | 2.19 | -3.60 | -1.41 | 0.14 | -0.19 | 7.40 | 13.80 | 0.34 |
| RV08 | 22 | M | 63 | 87 | 0.95 | -1.33 | -0.38 | 0.06 | -0.05 | 7.60 | 13.90 | 0.12 |
| RV03 | 28 | M | 66 | 84 | 1.60 | -2.38 | -0.78 | 0.11 | -0.10 | 8.10 | 14.70 | 0.22 |
| RV10 | 28 | F | 73 | 77 | 3.82 | -3.67 | 0.16 | 0.20 | -0.17 | 7.50 | 14.80 | 0.37 |
| RV01 | 29 | F | 85 | 65 | 4.82 | -2.27 | 2.55 | 0.23 | -0.19 | 5.00 | 13.50 | 0.42 |
| RV07 | 42 | F | 71 | 79 | 3.30 | -4.86 | -1.57 | 0.18 | -0.24 | 7.10 | 14.20 | 0.42 |
| RV04 | 44 | M | 66 | 84 | 0.43 | -0.66 | -0.24 | 0.04 | -0.05 | 6.60 | 13.20 | 0.09 |
| RV09 | 52 | M | 66 | 84 | 2.24 | -4.16 | -1.92 | 0.12 | -0.21 | 7.30 | 13.90 | 0.33 |
| RVO5 | 53 | M | 69 | 81 | 1.41 | -2.24 | -0.83 | 0.09 | -0.12 | 6.90 | 13.80 | 0.20 |
| | | | | | | | | | | | | |
| CP09 | 22 | F | 61 | 89 | 2.64 | -3.41 | -0.78 | 0.15 | -0.15 | 7.40 | 13.50 | 0.30 |
| CP05 | 26 | M | 72 | 78 | 10.10 | -6.44 | 3.66 | 0.56 | -0.37 | 6.90 | 14.10 | 0.93 |
| CP08 | 30 | M | 88 | 62 | 2.36 | -1.42 | 0.94 | 0.13 | -0.11 | 4.00 | 12.80 | 0.23 |
| CP06 | 25 | F | 64 | 86 | 1.05 | -1.36 | -0.31 | 0.07 | -0.07 | 8.50 | 14.90 | 0.14 |
| CP03 | 29 | F | 79 | 71 | 4.22 | -3.11 | 1.10 | 0.21 | -0.19 | 6.70 | 14.60 | 0.40 |
| CP02 | 42 | F | 68 | 82 | 1.09 | -1.88 | -0.79 | 0.08 | -0.09 | 6.80 | 13.60 | 0.17 |
| CP01 | 44 | M | 64 | 86 | 1.95 | -4.00 | -2.05 | 0.11 | -0.17 | 8.00 | 14.40 | 0.28 |
| CP04 | 52 | M | 66 | 84 | 3.08 | -4.44 | -1.36 | 0.17 | -0.18 | 8.20 | 14.80 | 0.35 |
| CP07 | 55 | M | 74 | 76 | 4.02 | -5.91 | -1.88 | 0.20 | -0.30 | 6.30 | 13.70 | 0.50 |
| | | | | | | | | | | | | |
| NC07 | 20 | F | 73 | 77 | 5.10 | -6.19 | -1.09 | 0.29 | -0.29 | 7.50 | 14.80 | 0.58 |
| NCO8 | 25 | M | 67 | 83 | 4.57 | -4.52 | 0.05 | 0.29 | -0.25 | 8.00 | 14.70 | 0.54 |
| NC05 | 27 | M | 67 | 83 | 0.95 | -0.92 | 0.03 | 0.07 | -0.05 | 7.10 | 13.80 | 0.12 |
| NC09 | 30 | F | 98 | 52 | 1.54 | -1.19 | 0.34 | 0.09 | -0.08 | 5.60 | 15.40 | 0.17 |
| NC03 | 30 | F | 75 | 75 | 0.59 | -1.18 | -0.59 | 0.08 | -0.09 | 8.20 | 15.70 | 0.17 |
| NC04 | 41 | F | 77 | 73 | 0.97 | -0.69 | 0.28 | 0.04 | -0.05 | 7.40 | 15.10 | 0.09 |
| NC06 | 46 | M | 65 | 85 | 4.66 | -7.65 | -2.98 | 0.26 | -0.33 | 7.70 | 14.20 | 0.59 |
| NC01 | 53 | M | 73 | 77 | 4.80 | -6.31 | -1.51 | 0.24 | -0.30 | 7.40 | 14.70 | 0.54 |
| NC02 | 53 | M | 81 | 69 | 0.21 | -0.23 | -0.02 | 0.01 | -0.02 | 3.30 | 11.40 | 0.04 |

**Cerebral Aqueduct Analysis of 150 slices (15 time points each divided into 10 slices)**
**At start of year**

## Cerebral Aqueduct Statistical Analysis at start of year

| **Net flow** | | | | | | |
|---|---|---|---|---|---|---|
| Friedman's ANOVA Table | | | | | | |
| Source | SS | Df | MS | Chi-sq | Prob>Chi-sq | |
| Columns | 1.5556 | 2 | 0.77778 | 1.5556 | 0.45943 | |
| Error | 16.4444 | 16 | 1.0278 | | | |
| Total | 18 | 26 | | | | |
| | | | | | | |
| **negative flow width proportion** | | | | | | |
| Friedman's ANOVA Table | | | | | | |
| Source | SS | Df | MS | Chi-sq | Prob>Chi-sq | |
| Columns | 2.7222 | 2 | 1.3611 | 2.8 | 0.2466 | |
| Error | 14.7778 | 16 | 0.92361 | | | |
| Total | 17.5 | 26 | | | | |
| | | | | | | |
| **dif between max +ve and -ve flow** | | | | | | |
| Friedman's ANOVA Table | | | | | | |
| Source | SS | Df | MS | Chi-sq | Prob>Chi-sq | |
| Columns | 0.22222 | 2 | 0.11111 | 0.22222 | 0.89484 | |
| Error | 17.7778 | 16 | 1.1111 | | | |
| Total | 18 | 26 | | | | |
| | | | | | | |
| **negative flow total** | | | | | | |
| Friedman's ANOVA Table | | | | | | |
| Source | SS | Df | MS | Chi-sq | Prob>Chi-sq | |
| Columns | 0.88889 | 2 | 0.44444 | 0.88889 | 0.64118 | |
| Error | 17.1111 | 16 | 1.0694 | | | |
| Total | 18 | 26 | | | | |
| | | | | | | |
| **positive flow total** | | | | | | |
| Friedman's ANOVA Table | | | | | | |
| Source | SS | Df | MS | Chi-sq | Prob>Chi-sq | |
| Columns | 0.66667 | 2 | 0.33333 | 0.66667 | 0.71653 | |
| Error | 17.3333 | 16 | 1.0833 | | | |
| Total | 18 | 26 | | | | |
| | | | | | | |
| **max systolic flow** | | | | | | |
| Friedman's ANOVA Table | | | | | | |
| Source | SS | Df | MS | Chi-sq | Prob>Chi-sq | |
| Columns | 0.22222 | 2 | 0.11111 | 0.22222 | 0.89484 | |
| Error | 17.7778 | 16 | 1.1111 | | | |
| Total | 18 | 26 | | | | |

SS = sum of squares df = degrees of freedom MS = mean square
(statistical software package used: MATLAB)

| | age y | Sex | No +ve div | No -ve div | Sum +ve ml/min | Sum –ve ml/min | net flow ml/min | max +ve ml/sec | max –ve ml/sec | 1st 0 cross | 2nd 0 cross | Max dif ml/sec |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| RV06 | 20 | F | 56 | 94 | 1.94 | -4.94 | -3.00 | 0.13 | -0.19 | 8.00 | 13.60 | 0.33 |
| RV08 | 22 | M | 56 | 94 | 0.57 | -1.21 | -0.64 | 0.05 | -0.05 | 8.40 | 14.00 | 0.11 |
| RV03 | 28 | M | 68 | 82 | 2.62 | -2.80 | -0.18 | 0.15 | -0.12 | 8.20 | 15.00 | 0.27 |
| RV10 | 28 | F | 71 | 79 | 2.94 | -3.41 | -0.47 | 0.15 | -0.17 | 8.20 | 15.30 | 0.32 |
| RV01 | 29 | F | 70 | 80 | 3.24 | -3.08 | 0.16 | 0.18 | -0.17 | 7.30 | 14.30 | 0.35 |
| RV07 | 42 | F | 70 | 80 | 2.55 | -4.57 | -2.01 | 0.15 | -0.21 | 6.80 | 13.80 | 0.36 |
| RV04 | 44 | M | 47 | 103 | 1.08 | -2.45 | -1.37 | 0.10 | -0.15 | 6.90 | 11.60 | 0.25 |
| RV09 | 52 | M | 74 | 76 | 3.10 | -3.18 | -0.09 | 0.15 | -0.15 | 7.30 | 14.70 | 0.30 |
| RVO5 | 53 | M | 71 | 79 | 3.36 | -2.48 | 0.88 | 0.18 | -0.12 | 7.40 | 14.50 | 0.30 |
| | | | | | | | | | | | | |
| CP09 | 22 | F | 61 | 89 | 2.63 | -3.38 | -0.75 | 0.15 | -0.15 | 7.40 | 13.50 | 0.30 |
| CP05 | 26 | M | 72 | 78 | 10.57 | -7.22 | 3.35 | 0.60 | -0.50 | 7.20 | 14.40 | 1.10 |
| CP08 | 30 | M | 88 | 62 | 2.29 | -1.39 | 0.90 | 0.12 | -0.10 | 4.00 | 12.80 | 0.23 |
| CP06 | 25 | F | 7 | 143 | 0.00 | -1.53 | -1.53 | 0.00 | -0.06 | 15.90 | 16.60 | 0.07 |
| CP03 | 29 | F | 79 | 71 | 4.24 | -3.13 | 1.10 | 0.21 | -0.20 | 6.70 | 14.60 | 0.40 |
| CP02 | 42 | F | 73 | 77 | 1.46 | -1.49 | -0.03 | 0.10 | -0.09 | 7.50 | 14.80 | 0.19 |
| CP01 | 44 | M | 63 | 87 | 2.23 | -4.51 | -2.28 | 0.14 | -0.21 | 8.00 | 14.30 | 0.34 |
| CP04 | 52 | M | 67 | 83 | 2.85 | -4.14 | -1.29 | 0.16 | -0.20 | 8.10 | 14.80 | 0.36 |
| CP07 | 55 | M | 83 | 67 | 5.84 | -7.39 | -1.56 | 0.25 | -0.47 | 5.80 | 14.10 | 0.73 |
| | | | | | | | | | | | | |
| NC07 | 20 | F | 73 | 77 | 5.27 | -6.28 | -1.00 | 0.28 | -0.30 | 7.50 | 14.80 | 0.58 |
| NCO8 | 25 | M | 67 | 83 | 3.57 | -5.27 | -1.70 | 0.19 | -0.23 | 8.00 | 14.70 | 0.42 |
| NC05 | 27 | M | 68 | 82 | 1.15 | -1.47 | -0.32 | 0.07 | -0.08 | 7.10 | 13.90 | 0.15 |
| NC09 | 30 | F | 38 | 112 | 0.11 | -0.65 | -0.54 | 0.01 | -0.02 | 9.40 | 13.20 | 0.04 |
| NC03 | 30 | F | 75 | 75 | 4.35 | -3.27 | 1.08 | 0.22 | -0.17 | 8.10 | 15.60 | 0.39 |
| NC04 | 41 | F | 70 | 80 | 1.97 | -2.14 | -0.17 | 0.11 | -0.14 | 7.50 | 14.50 | 0.25 |
| NC06 | 46 | M | 69 | 81 | 5.57 | -7.24 | -1.66 | 0.30 | -0.35 | 7.50 | 14.40 | 0.65 |
| NC01 | 53 | M | 73 | 77 | 5.11 | -6.23 | -1.12 | 0.25 | -0.28 | 7.30 | 14.60 | 0.53 |
| NC02 | 53 | M | 61 | 89 | 0.34 | -0.91 | -0.56 | 0.02 | -0.04 | 8.20 | 14.30 | 0.06 |

**Cerebral Aqueduct Analysis of 150 slices (15 time points each divided into 10 slices)**
**At end of year**

## Cerebral Aqueduct Statistical Analysis at end of year

| **net flow** | | | | | | |
|---|---|---|---|---|---|---|
| Friedman's ANOVA Table | | | | | | |
| Source | SS | Df | MS | Chi-sq | Prob>Chi-sq | |
| Columns | 0.66667 | 2 | 0.33333 | 0.66667 | 0.71653 | |
| Error | 17.3333 | 16 | 1.0833 | | | |
| Total | 18 | 26 | | | | |
| | | | | | | |
| **negative flow width proportion** | | | | | | |
| Friedman's ANOVA Table | | | | | | |
| Source | SS | Df | MS | Chi-sq | Prob>Chi-sq | |
| Columns | 2 | 2 | 1 | 2.1176 | 0.34686 | |
| Error | 15 | 16 | 0.9375 | | | |
| Total | 17 | 26 | | | | |
| | | | | | | |
| **dif between max +ve and -ve flow** | | | | | | |
| Friedman's ANOVA Table | | | | | | |
| Source | SS | Df | MS | Chi-sq | Prob>Chi-sq | |
| Columns | 0.22222 | 2 | 0.11111 | 0.22222 | 0.89484 | |
| Error | 17.7778 | 16 | 1.1111 | | | |
| Total | 18 | 26 | | | | |
| | | | | | | |
| **negative flow total** | | | | | | |
| Friedman's ANOVA Table | | | | | | |
| Source | SS | Df | MS | Chi-sq | Prob>Chi-sq | |
| Columns | 0.66667 | 2 | 0.33333 | 0.66667 | 0.71653 | |
| Error | 17.3333 | 16 | 1.0833 | | | |
| Total | 18 | 26 | | | | |
| | | | | | | |
| **positive flow total** | | | | | | |
| Friedman's ANOVA Table | | | | | | |
| Source | SS | Df | MS | Chi-sq | Prob>Chi-sq | |
| Columns | 0.66667 | 2 | 0.33333 | 0.66667 | 0.71653 | |
| Error | 17.3333 | 16 | 1.0833 | | | |
| Total | 18 | 26 | | | | |
| | | | | | | |
| **max systolic flow** | | | | | | |
| Friedman's ANOVA Table | | | | | | |
| Source | SS | Df | MS | Chi-sq | Prob>Chi-sq | |
| Columns | 0.22222 | 2 | 0.11111 | 0.22222 | 0.89484 | |
| Error | 17.7778 | 16 | 1.1111 | | | |
| Total | 18 | 26 | | | | |

SS = sum of squares df = degrees of freedom MS = mean square
(statistical software package used: MATLAB)

## Carotid Basilar Blood Flow mls/min

| | 1a | 1b | 2a | 2b | difs1a1b | dif2a2b | mean 1a1b | mean2a2b | Diff means |
|---|---|---|---|---|---|---|---|---|---|
| RV05 | 1076.53 | 1042.12 | 1075.51 | 835.07 | 34.41 | 240.44 | 1059.32 | 955.29 | 104.03 |
| RV04 | 919.44 | 816.58 | 745.30 | 766.03 | 102.86 | -20.73 | 868.01 | 755.66 | 112.35 |
| RV09 | 701.70 | 654.45 | 644.33 | 643.84 | 47.25 | 0.48 | 678.08 | 644.08 | 33.99 |
| RV01 | 1015.18 | 911.69 | 756.79 | 726.88 | 103.49 | 29.92 | 963.44 | 741.84 | 221.60 |
| RV03 | 998.75 | 1096.34 | 1290.01 | 1175.96 | -97.59 | 114.05 | 1047.54 | 1232.98 | -185.44 |
| RV07 | 1512.63 | 1486.12 | 1287.51 | 1316.20 | 26.51 | -28.70 | 1499.37 | 1301.85 | 197.52 |
| RV06 | 927.07 | 855.20 | 945.85 | 838.36 | 71.86 | 107.50 | 891.13 | 892.11 | -0.97 |
| RV10 | 741.55 | 739.27 | 855.50 | 936.77 | 2.28 | -81.26 | 740.41 | 896.13 | -155.72 |
| RV08 | 672.13 | 708.29 | 513.21 | 481.65 | -36.16 | 31.56 | 690.21 | 497.43 | 192.78 |
| | | | | | | | | | |
| CP06 | 1203.19 | 1181.51 | 1222.73 | 1192.69 | 21.68 | 30.04 | 1192.35 | 1207.71 | -15.36 |
| CP09 | 1483.39 | 1103.06 | 1232.00 | 1135.42 | 380.34 | 96.58 | 1293.22 | 1183.71 | 109.52 |
| CP05 | 841.09 | 822.54 | 1063.06 | 966.15 | 18.55 | 96.91 | 831.81 | 1014.60 | -182.79 |
| CP08 | 1071.07 | 1165.46 | 1492.52 | 1531.66 | -94.39 | -39.14 | 1118.26 | 1512.09 | -393.82 |
| CP03 | 1185.69 | 1153.60 | 1277.21 | 1394.83 | 32.09 | -117.62 | 1169.64 | 1336.02 | -166.37 |
| CP01 | 1582.16 | 1630.21 | 1694.07 | #DIV/0! | -48.05 | #DIV/0! | 1606.18 | 1694.07 | -87.89 |
| CP02 | 1156.22 | 854.28 | 1190.71 | 1199.01 | 301.93 | -8.30 | 1005.25 | 1194.86 | -189.61 |
| CP04 | 903.15 | 1016.39 | 989.71 | 967.82 | -113.24 | 21.89 | 959.77 | 978.76 | -18.99 |
| CP07 | 1229.58 | 1217.83 | 1188.41 | 1127.43 | 11.75 | 60.98 | 1223.70 | 1157.92 | 65.78 |
| | | | | | | | | | |
| NC01 | 1126.24 | 1085.58 | 1478.74 | 1362.36 | 40.66 | 116.37 | 1105.91 | 1420.55 | -314.64 |
| NC02 | 1078.51 | 913.68 | 878.26 | 727.58 | 164.83 | 150.68 | 996.10 | 802.92 | 193.18 |
| NC04 | 1102.70 | 954.51 | 1229.17 | 1099.28 | 148.19 | 129.89 | 1028.60 | 1164.23 | -135.63 |
| NC06 | 1265.65 | 1007.45 | 1111.82 | 1166.75 | 258.20 | -54.93 | 1136.55 | 1139.28 | -2.74 |
| NC05 | 1185.85 | 1034.08 | 1388.48 | 1163.54 | 151.76 | 224.94 | 1109.97 | 1276.01 | -166.04 |
| NC09 | 1073.88 | 1372.72 | 1161.82 | 1172.69 | -298.84 | -10.86 | 1223.30 | 1167.26 | 56.04 |
| NC07 | 960.99 | 958.00 | 1400.87 | 1075.57 | 2.99 | 325.29 | 959.49 | 1238.22 | -278.73 |
| NC03 | 1198.25 | 1371.70 | 1123.70 | 1177.19 | -173.45 | -53.49 | 1284.98 | 1150.45 | 134.53 |
| NC08 | 1026.49 | 894.80 | 922.95 | 926.69 | 131.69 | -3.75 | 960.64 | 924.82 | 35.82 |

| -15.3623 | -314.644 | Friedman's ANOVA Table | | | | | |
|---|---|---|---|---|---|---|---|
| 109.5158 | 193.1756 | Source | SS | MS | Chi-sq | Prob>Chi-sq | |
| -182.789 | -135.625 | Columns | 22.2222 | 11.1111 | 2.963 | 0.2273 | |
| -393.824 | -2.73764 | Interaction | 7.1111 | 1.7778 | | | |
| -166.375 | -166.043 | Error | 150.6667 | 8.3704 | | | |
| -87.8859 | 56.04426 | Total | 180 | | | | |
| -189.611 | -278.73 | Test for column effects after row effects are removed | | | | | |
| -18.9906 | 134.5274 | | | | | | |
| 65.78453 | 35.82181 | | | | | | |

**Statistical Analysis of Carotid Basilar blood flow**
(Statistical software package used: MATLAB)

# APPENDIX A12: EMG data

| Treated group | | | Frequency/Hz | | | |
|---|---|---|---|---|---|---|
| Code rv | 1a | 1b | Frequency shift at start 1a-1b | 2a | 2b | Frequency shift at end 2a-2b |
| 1 | 51 | 43 | 8 | 40 | 39 | 1 |
| 2 | 41 | 45 | -4 | | | |
| 3 | 78 | 72 | 6 | 57 | 51 | 6 |
| 4 | 70 | 67 | 3 | 39 | 35 | 4 |
| 5 | 51 | 49 | 2 | 43 | 41 | 2 |
| 6 | 51 | | | 49 | 37 | 12 |
| 7 | 49 | 49 | 0 | 47 | 49 | -2 |
| 8 | 53 | | | | | |
| 9 | 76 | 71 | 5 | 57 | 55 | 2 |
| 10 | 53 | 53 | 0 | 47 | 45 | 2 |
| **mean** | **57** | **56** | **3** | **47** | **44** | **3** |
| **sd** | **13** | **12** | **4** | **7** | **7** | **4** |
| | | | p = | 0.305854 | | |
| | | | | | | |
| | | | lemg/ micro-Volt seconds | | | |
| rv | 1a | 1b | 1a-1b | 2a | 2b | 2a-2b |
| 1 | 5.59E+02 | 4.94E+02 | -65 | | | 0 |
| 2 | 5.33E+02 | 5.57E+02 | 24 | | | |
| 3 | | 5.77E+02 | | 6.15E+02 | 5.60E+02 | -55 |
| 4 | | 4.03E+02 | | 2.36E+02 | 3.77E+02 | 140 |
| 5 | 7.20E+02 | 6.98E+02 | -23 | 9.48E+02 | 9.57E+02 | 9 |
| 6 | 5.46E+02 | 5.57E+02 | 11 | 3.55E+02 | 4.78E+02 | 124 |
| 7 | 4.95E+02 | 5.48E+02 | 53 | 6.12E+02 | 6.92E+02 | 80 |
| 8 | 5.43E+02 | | | 4.80E+02 | 4.40E+02 | -40 |
| 9 | 3.96E+02 | 5.08E+02 | 111 | 6.98E+02 | 7.31E+02 | 33 |
| 10 | 4.48E+02 | 6.20E+02 | 172 | 4.68E+02 | 4.92E+02 | 24 |
| **mean** | **530** | **551** | **40** | **551** | **591** | **35** |
| **sd** | **95** | **82** | **80** | **219** | **191** | **68** |
| | | | p = | 0.962408 | | |

**Frequency shift and integrated electromyography data on treated group**

(Statistical software package used: SPSS for Windows)

| Cfs/me Control group | | | Frequency/Hz | | | |
|---|---|---|---|---|---|---|
| Code cp | 1a | 1b | Frequency shift at start 1a-1b | 2a | 2b | Frequency shift at end 2a-2b |
| 1 | 47 | 39 | 8 | 51 | 49 | 2 |
| 2 | 43 | 39 | 4 | 38 | 39 | -1 |
| 3 | 37 | 36 | 1 | 45 | 26 | 19 |
| 4 | 38 | 38 | 0 | 41 | 36 | 5 |
| 5 | 43 | 45 | -2 | | | |
| 6 | | | | | | |
| 7 | | | | | | |
| 8 | 57 | 57 | 0 | 57 | 49 | 8 |
| 9 | | | | | | |
| 10 | | | | | | |
| **mean** | **44** | **42** | **2** | **46** | **40** | **7** |
| **sd** | **7** | **8** | **4** | **8** | **10** | **8** |
| | | | p = | 0.418433 | | |
| | | | | | | |
| | | | lemg/ micro-Volt seconds | | | |
| cp | 1a | 1b | | 2a | 2b | |
| 1 | 7.28E+02 | 7.68E+02 | 40 | 4.89E+01 | 6.31E+01 | 14 |
| 2 | 3.11E+02 | 2.90E+02 | -20 | 3.28E+02 | 3.97E+02 | 70 |
| 3 | 1.71E+02 | 1.55E+02 | -16 | 2.27E+02 | 2.34E+02 | 7 |
| 4 | 4.97E+02 | 4.44E+02 | -53 | 3.45E+02 | 3.61E+02 | 16 |
| 5 | 9.12E+02 | 8.56E+02 | -56 | | | |
| 6 | | | | | | |
| 7 | | | | | | |
| 8 | 6.15E+02 | 6.60E+02 | 45 | 5.70E+02 | 5.15E+02 | -55 |
| 9 | | | 0 | | | 0 |
| 10 | | | 0 | | | 0 |
| **mean** | **539** | **529** | **-7** | **304** | **314** | **7** |
| **sd** | **272** | **278** | **37** | **190** | **172** | **36** |
| | | | p = | 0.748303 | | |

**Frequency shift and integrated electromyography data on untreated cfs/me group**

(Statistical software package used: SPSS for Windows)

| Healthy control group | | | Frequency/Hz | | | |
|---|---|---|---|---|---|---|
| Code nc | 1a | 1b | Frequency shift at start 1a-1b | 2a | 2b | Frequency shift at end 2a-2b |
| 1 | 47 | 49 | -2 | 36 | 30 | 6 |
| 2 | 54 | 54 | 0 | 43 | 37 | 6 |
| 3 | 41 | 45 | -4 | 43 | 39 | 4 |
| 4 | 51 | 43 | 8 | 43 | 45 | -2 |
| 5 | 45 | 45 | 0 | 37 | 45 | -8 |
| 6 | 45 | 57 | -12 | | | |
| 7 | 53 | 51 | 2 | 45 | 45 | 0 |
| 8 | 39 | 49 | -10 | 47 | 43 | 4 |
| 9 | 49 | 45 | 4 | 47 | 45 | 2 |
| 10 | | | | | | |
| **mean** | **47** | **49** | **-2** | **43** | **41** | **2** |
| **sd** | **5** | **5** | **6** | **4** | **5** | **5** |
| | | | p = | 0.579255 | | |
| | | | | | | |
| | | | lemg | | | |
| nc | 1a | 1b | | 2a | 2b | |
| 1 | 3.86E+02 | 3.74E+02 | -12 | 2.22E+02 | 2.50E+02 | 29 |
| 2 | 8.33E+02 | 7.99E+02 | -33 | 7.40E+02 | 6.30E+02 | -110 |
| 3 | 5.75E+02 | 6.48E+02 | 73 | 4.08E+02 | 5.01E+02 | 93 |
| 4 | 5.33E+02 | 3.30E+02 | -203 | 3.50E+02 | 2.47E+02 | -103 |
| 5 | 5.30E+02 | 5.57E+02 | 27 | 6.74E+02 | 7.08E+02 | 35 |
| 6 | 5.78E+02 | 6.86E+02 | 108 | | | |
| 7 | 6.26E+02 | 7.29E+02 | 103 | 8.44E+02 | 7.21E+02 | -123 |
| 8 | 4.74E+02 | 4.47E+02 | -27 | 4.49E+02 | 4.00E+02 | -50 |
| 9 | 7.45E+02 | 7.97E+02 | 52 | 5.60E+01 | 6.66E+01 | 11 |
| 10 | | | | | | |
| **mean** | **587** | **597** | **10** | **468** | **440** | **-27** |
| **sd** | **135** | **178** | **96** | **269** | **240** | **80** |
| | | | p = | 0.495906 | | |

**Frequency shift and integrated electromyography data on Healthy control group**

(Statistical software package used: SPSS for Windows)

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## PUBLICATIONS ARISING FROM THIS THESIS

Parts of this thesis have been published or submitted for publication as follows:

Perrin RN, 1993. Chronic fatigue syndrome: a review from the biomechanical perspective. B*ritish Osteopathic Journal*. 11: 15-23.

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