THE EFFECTS OF SELENIUM SUPPLEMENTATION ON THE MOOD STATES OF CHRONIC FATIGUE SYNDROME AND HEALTHY CONTROL SUBJECTS

A thesis
submitted in partial fulfilment
of the requirements for the degree
of
Master of Science in Psychology

by

Boyd Hansley Scott

University of Canterbury

February 1993

TABLE OF CONTENTS

TABLE OF FIGURES

ABSTRACT

Thirty three subjects diagnosed with Chronic Fatigue Syndrome and 37 healthy matched controls were paired and given either selenium or neutral supplementation to take for six weeks. Blood testing before and after completion of the trials confirmed changes in selenium blood levels. All subjects completed the Profile Of Mood States (POMS) and Beck Depression Inventory (BDI) Questionnaires on three occasions. Mood scores and BDI scores were analyzed and results indicate a marked increase in mood for CFS subjects on selenium compared to CFS subjects on placebo. There was no significant mood change for controls on either treatment. Analysis of the 6 POMS sub-scores also revealed that CFS mood profile was different from the mood profile of healthy controls.

ACKNOWLEDGEMENTS

I would like to thank many kind people and organisations for their generous assistance in the development and execution of this Thesis.

I am very grateful to all subjects and their families for their willing participation in what was a time consuming and drawn out exercise. I am also very grateful to the support of the M.E. Societies in Dunedin, Oamaru and Timaru. Their help in recruiting members for the study was extremely valuable.

I am very grateful and extremely thankful in more ways than can be expressed here to my Supervisor Dr Dalrymple-Alford for the valuable ideas he shared, the perseverance he showed and the sound guidance he provided in keeping this programme going even when the novelty of research was fading and the pressure of other responsibilities were starting to affect the present author. I learnt much from his notes, his comments on the script and the many long distance conversations we had on everything from computers to statistics and sometimes his own experience on matters of research.

I would also like to sincerely thank the Hospital Boards

and Laboratory staff in Dunedin, Oamaru and Timaru for their generous assistance with the blood testing programme. In particular, I am very grateful to Mr Walmsley and his staff in Pathology, Princess Margaret Hospital in Christchurch for the excellent job of analysing the blood samples.

I would also like to thank my family, especially my wife for the support she gave in preparing the programme and assisting with the task of testing and marking the numerous schedules, and my son Gregory for his help with the computer programme.

Finally we gratefully acknowledge the generous support of Vitafit- Megavitamin Laboratories and Dr W Stewart, Christchurch, in providing both the supply of tablets and financial assistance to complete this research.

Chapter 1 INTRODUCTION

The purpose of this study was to examine the effect of selenium supplementation on the general mood states of both Chronic Fatigue Syndrome (CFS) subjects (a condition also known as Myalgic encephalomyelitis or ME) and healthy Non-CFS subjects acting as controls. Before we examine the current understanding on the condition of CFS, some explanation of the controversy over the use of the term ME needs to be made. This will help to put into perspective the often strange difficulties that some of the research findings have generated both for those in the medical profession and those who have been diagnosed as having CFS.

1.01 Historical Perspective

Historically, the term ME was first used by Dr Ramsay in 1956, following the appearance of the Royal Free Disease epidemic in London (Ramsay 1988). His medical report described the symptoms of ME as characterized by nervous abnormalities (facial paralysis, difficulty in swallowing, severe muscle pain and loss of skin sensitivity (hypaesthesia). Unfortunately, scientific attempts at the time to discover the cause or causes did not have any

success. Similar epidemics with basically the same symptoms were known to have occurred as early as 1934 (in the USA) and were variously named Endemic Neuromyasthenia, Royal Free Disease, Post Infectious Neuromyasthenia, Chronic Mononucleosis, Chronic Epstein Barr Virus disease (CEBV), Post Viral Fatigue syndrome and Chronic Fatigue Syndrome (even "Yuppie Flu"). It is important to note that the major characteristic features of these syndromes were muscle fatigue, pain and experiences of tiredness on exertion and depressive thought patterns related to psychological disturbances (Murdoch 1988, Behan 1981).

1.02 ME or CFS - A CONTROVERSY

In 1985, at Lake Tahoe (Nevada), an epidemic of similar nature brought more urgent attention to the issue of CFS recognition. But again the follow up checks made at Lake Tahoe to identify possible causes were not successful. The media reported these epidemics as flu-like temporary infections that were soon to pass. However, a more careful examination of patients immune system soon revealed a higher than normal level of antibodies (Murdoch 1988), implying an exposure to some sort of pathogen. This finding intensified the search for signs of Epstein Barr Virus (EBV), a virus commonly associated with glandular fever. Again, no conclusive result was reached, but the investigation did reveal apparent defects in the

immune system (Fark 1990). In the media, such outbreaks were labelled as Chronic Epstein Barr Virus (CEBV) epidemics. Yet the symptoms of CEBV were considered to be the same as for Chronic Fatigue Syndrome (CFS) because both referred to the same characteristic group of symptoms (syndrome). However, those in the forefront of this research were somewhat hesitant to confirm or even acknowledge that the etiology of chronic fatigue somehow derives from the presence of EBV in body tissue. However, the symptoms of "Chronic Fatigue" can be traced to muscle pathology but the term "Myalgic encephalomyelitis" suggests a nervous and muscular disorder which has not yet been verified by pathologists. Nor has there been any useful diagnosis of psychological or psychiatric disorder that includes the major symptoms of the CFS syndrome. Because of this uncertainty, the term CFS became more acceptable to scientists (Holmes, et al 1988) since it clearly describes an identifiable feature of the syndrome, rather than suggesting a possible cause that is not yet known. Hence the empirical nature of the CFS label was attracting a more positive response from the scientific community than the ME label. But basically, the medical profession are referring to the same set of symptoms or syndrome no matter which term is used. Abbey and Garfinkel (1990) have pointed out that the Americans and Canadians have only recently accepted the CFS term but the world wide support groups still prefer Myalgic

encephalomyelitis (ME) because CFS is considered to be a trivialisation of the ME condition.

The medical profession is therefore not always in uniform agreement or support of the various diagnoses available for a number of reasons. The most important is the lack of empirical medical data to provide a basis for the diagnosis. As a result, many practitioners would not have anything to do with attempts to diagnose the CFS syndrome. In the Otago region, most medical practitioners would refer patients on to the School of General Practice (Otago Medical School) for Professor Murdoch to assess diagnosis of a CFS syndrome. But in a recent article (Otago Daily Times 6 May 1992), Murdoch was quoted as saying that his efforts to develop a definitive and acceptable diagnosis for the syndrome has not always been well received by the medical profession. Not all members of the profession can totally agree with the emphasis placed on the environment as an important factor in the development of the CFS condition. Murdoch seems to believe that the present medical crisis of increasing human vulnerability to viral and immunological dysfunctions (e.g AIDS) is partly due to a deteriorating world wide environment.

As already pointed out, the controversy associated with the study of CFS is linked to the presence of many versions and labels for the condition, each with its own

variation in emphasis. In this thesis, I shall remain impartial to the controversy and from here on, the label CFS shall be used to refer to the same syndrome referred to as ME - but the latter term will be used where it has been accepted in those reports being discussed in the current thesis.

All CFS subjects chosen for this study were either diagnosed by Professor Murdoch (Department of General Practice, Otago Medical School) or other medical practitioners who later refers the case to Murdoch for confirmation. Unfortunately the diagnosis of CFS is not always a clear-cut matter but there does appear to be a growing confidence amongst some GP's that despite the lack of empirical data, the often debilitating nature of the condition does require a more sympathetic approach. Besides that, there is also a growing acceptance by the media and the public (as a result of efforts by the various support groups like the ME Society) that the CFS condition is real - even if it was still without conclusive evidence that might convince the scientific community but in particular the medical profession.

1.03 THE RECURRENT FEATURES OF CFS

ME, according to Murdoch's (1987) clinical survey, is characterized by a number of recurring features. These

are mainly symptoms of irritability, emotional stress, palpitation and abdominal difficulties. ME subjects have also been identified on the basis that the syndrome they presented involved:

1. a short history of illness lasting more than three months.
2. a recurrent pattern of illness relapses.
3. a recurrent pattern of exhaustion, muscle pain and weakness during exercise.

A similar pattern of symptoms have been generally accepted and used for diagnostic purposes elsewhere (Prasher et al 1990). The symptoms are not difficult to recognise and some practitioners who make the attempt to diagnose seem to have little difficulty recognising the condition. The problem is to distinguish these symptoms from those of many other conditions. Hence, there are many uncertainties about the basic nature of the condition. Some believe it is psychiatric in nature (McEvedy & Beard 1973). Some consider it to be a physiological problem relating to current infections or immune dysfunctions - i.e a medical problem (Lynch et al 1989). These uncertainties have lead scientists to a number of investigations that has generated various reports and debates. The most significant of these debates is centred around the cause of the CFS condition. In the following section we will examine this very debate and

consider not only the attention given by the medical profession but also that by the public and support groups of CFS/ME sufferers.

1.04 MEDICAL OR PSYCHOLOGICAL PROBLEM ?

The literature by both CFS sufferers (Horne 1991) and health professionals (McIntyre 1989, Shepherd 1989) reflects a common concern at the lack of supportive data for establishing ME as a bonafide medical condition. Some have suggested "its all in the mind" (McEvedy, et al 1978) or that sufferers were mentally disturbed (Kroenke 1991). Those who withdraw from the work force, as a consequence of their illness, are sometimes accused of malingering. In her Thesis, Sylvia Horne (1990) describes the traumatic daily experiences of the ME sufferer as the "daily battle with despair." The despair is generated from the experience of disbelief and shock that CFS sufferers discover when they try unsuccessfully to share their problems with unsympathetic health authorities or colleagues (and sometimes unhelpful family members). The general lack of professional recognition of this illness adds more pressure on those already diagnosed by some practitioners as having the syndrome. Psychiatrists (McEvedy et al 1973) have suggested a diagnosis of psychological dysfunction in some instances of CFS epidemics. But this diagnosis is based on conceptual

rationalisations developed from the belief that sufferers have unresolved inner conflicts and emotional stresses. Unfortunately this approach so far seems far less convincing than the condition itself.

Most CFS sufferers and medical practitioners do not share this view which is accepted by some Psychiatrists. However efforts to evaluate significant psychological elements in CFS are being pursued in order to understand the psychological parameters of the condition. Recently some important findings with mood studies and depression in patients diagnosed as having CFS have been reported.

1.05 MOOD DISORDERS AND COGNITIVE DEFICITS IN CFS SUBJECTS

The incidence of mood disorders amongst CFS subjects is always a matter of great concern and one that needs careful attention.

Surprisingly, relatively little has actually been done to determine the psychological correlates of the CFS condition. However, as the following report shows, psychiatric and psychological disorders have been identified in some CFS sufferers.

A retrospective analysis of CFS patient history has indicated the possibility of psychiatric disorders

preceding the onset of the chronic fatigue syndrome. Kruesi et al (1989) used the National Institute of Mental Health Diagnostic Interview Schedule (NIMH/DIS) to study the lifetime prevalence of psychiatric disorders in 28 patients classified as having CFS. The results from these subjects were compared to those obtained from chronically and medically ill patients and from healthy individuals. The comparison revealed that the rate of psychiatric illness (phobia,somatization,depressive and panic disorders) amongst CFS subjects was higher than for the healthy and medically ill(non-psychiatric) group. Kruesi concludes that psychiatric disorders amongst CFS subjects seem to occur more often before rather than after they were diagnosed with CFS. In particular, it would appear that the CFS syndrome may be linked to psychiatric disorders like depression.

In their examination of 100 CFS patients, Manu et al (1989), found a consistent prevalence of depressive mood disorders in the group as a whole. This finding was also based on patients' medical history and evaluation of psychological profiles from the NIMH/DIS and Beck Depression Inventory (BDI) scores. The study examined each patient's history, physical and laboratory findings. From this examination, it was found that twenty-three of forty-four CFS subjects with depressive illness had experienced their first depressive episode before they

were diagnosed as having CFS. The overall findings however were only modest in distinguishing the severity of CFS group from the Non-CFS group that also experienced depression. Again, Manu concludes that not only were the signs of depressive illness an important precursor to the CFS syndrome. One outcome of this research is the suggestion that there may be a psychological component that predates the onset of CFS. This suggestion was carefully examined in the important studies that follow.

Taerk (1987) who examined the prevalence of a depressive disorder and symptoms in 24 subjects with neuromyasthenia (using the BDI) also found 67% had major depression.

Hickie et al (1990), found signs of depression in 45 of 48 CFS subjects, but their findings suggested that depression arose as a consequence of developing CFS rather than precipitating the occurrence of CFS. Of the 45 CFS patients that Hickie et al studied, 24 were diagnosed with non-endogenous depression and this was sometimes associated with mild forms of panic disorders. There were no cases of generalised anxiety disorders although a few reported simple phobias and one serious case of somatisation disorder (Briquet's disorder). According to Hickie, the pattern of current symptom and history of psychiatric disturbances in CFS patients is not the same as that shown by NON-CFS psychiatric patients. CFS

patients did not have the high pre- morbid rate of psychiatric disorders seen in other psychiatric patients. They were also less neurotic and at their worst, did not display the psychometric profile of non-endogenous depressive comparison group studied by these workers. Also there seemed to be no evidence that the CFS condition is some form of somatic representation of an underlying psychological condition. Hickie's use of the Eysenck Personality Inventory (EPI) and general health questionnaire also significantly concluded that CFS subjects were less neurotic in behaviour than psychiatric patients with neurotic conditions.

Prasher, et al (1990) reported that CFS patients may have deficits in the areas of cognitive and sensory perception. In this investigation, the assumption was made that CFS subjects may experience some form of sensory and cognitive disturbance which could be associated with neural deficits. To examine this assumption synchronous neural activity involving specific stimulus material was measured using two types of evoked potentials, sensory potentials for brain-stem, visual and somatosensory changes .
Firstly, sensory evoked potential readings were made in three separate areas. Readings from Brainstem potentials that were generated by alternating polarity click stimulation at 10 Hz with electrodes placed on the forehead. Visual potentials were recorded from visual

observations of a checkerboard pattern reversal stimulus generated by the Mistral system. Somatosensory potentials were also recorded from median nerve stimulation by cervical spine (Cv2) electrode stimulation.

Secondly, cognitive evoked potentials were elicited by two auditory discrimination tasks that involved subjects responding to either frequency or varying duration of tone. Subjects' task was to react to a target tone by pressing a response button as quickly as possible. The time taken to react were recorded as measures of responses.

This examination of multi-modality sensory-evoked potentials in CFS subjects found attention deficits and slower speed of information processing in CFS subjects. In the area of endogenous event-related potentials, cognitive potentials related to frequency and duration responses appear to be absent or significantly delayed in 52% of CFS patients. This would appear to support the widely acknowledged CFS complaint of cognitive impairment in the areas of memory disturbances and lack of ability to concentrate. However, the main concern by Prasher et al was to identify any differences in evoked potentials in both CFS and non-CFS subjects. Clearly in the area of sensory potentials of the visual, auditory brainstem and median nerve somatosensory systems, CFS subjects seemed

unaffected. This finding would therefore support the view that CFS subjects do not appear to suffer any biological disorder of the Central Nervous System . This distinction is important in that it is somewhat in contrast to abnormal sensory evoked potentials in subjects with multiple sclerosis - subjects who often display symptoms of CFS during the early phase of the development of multiple sclerosis.

Recently, Smith (1992) summarized two British studies (in press) that investigated memory ,attention and motor function in CFS subjects using a questionnaire/survey method and objective testing to assess emotional behaviour aspects and performance characteristics of CFS and control subjects. The findings indicate CFS subjects expressed concentration problems, memory impairments, higher levels of anxiety, somatic problems and depressions. They also found evidence of slower motor performance , memory deficits, increased visual sensitivity on various objective tests including impaired reaction times, poorer word recognition and free re-call primacy as well as impaired logical reasoning. However their evidence suggested that these impairments were unlikely to reflect global intellectual functioning impairments or that the performance impairment might be the result of depression.

There may be little doubt that people who suffer prolonged

bouts of neuromuscular pain, constant alimentary dysfunctions and experience recurring memory lapses that in the end may succumb to some form of psychological illness and at worse, perhaps develop a psychiatric condition relating to stress.

Many other workers emphasise the possibility of a somatic basis involving pathogens and the immune system rather than a psychiatric or neurological dysfunction. Hence the role of virus and the immune system is an important aspect of the study of the CFS syndrome.

1.06 VIRUSES AND THE IMMUNE SYSTEM

In the USA, persistent efforts by medical practitioners dealing with CFS led researchers to re-examine the question of viral infections identified in earlier studies of CFS patients. It is perhaps worth noting that the technical and scientific developments in the discipline of virology and immunology have been partly responsible for the increasing acceptability of CFS as a condition worthy of medical attention. At best, the study of viruses and how they can be controlled is difficult enough. But attempts to link its presence with CFS has been a more difficult task. Never the less there have been some important breakthroughs reported by Murdoch and Behan including a recent success in the USA with virus

implicated in CFS studies.

One of the suspected viral elements is a retrovirus, a relative of the kind that causes AIDS. These retroviruses contain the enzyme reverse transcriptase that converts viral RNA into cytoplasmic DNA either from extrachromosomal sites or from within the host cell nucleus where it coordinates activities within the cell DNA. Unfortunately, all three categories of retrovirus seem to have a natural affinity for attacking T4 lymphocytes (inducer/helper cells) and this will invariably lead to an imbalance in the ratio of T4:Ts suppressor cells, thus creating difficulties within the immune system. These difficulties arise because the Ts suppressor will act to suppress the immune system in the absence of sufficient regulatory T-Helpers that co-ordinate production of more anti-bodies. The two groups of viruses of major concern in current CFS research are the cytomegalovirus and the enterovirus.

1.06.A PERSISTENT (LATENT) CYTOMEGALOVIRUS

The most frequently occurring latent virus identified in CFS patients is the Epstein-Barr virus. A persistently high EB virus capsid IgG titre value (which indicates presence of the EB virus) was found in a CFS patient, who had ten years earlier suffered illness following an

initial chronic condition of viral infection (Shepherd 1989). However, to complicate matters, it is also known that EBV capsid IgG titre values may be the product of constant reinfections due to latent EB virus in the throat tissues (Shepherd 1989). The problem here may be twofold. Firstly, the possibility of a persistent viral infection that induces illness, or secondly, the partial destruction of the body's immune system such that the individual is unable to deal with the body's daily contact with pathogens.

The pathology of Epstein-Barr virus and its effect on the immune system of carriers were closely re-examined for a possible cause of the ME condition. Holmes (personal communication), has indicated that there is sufficient evidence to seriously suspect immune dysfunction as a prime cause of the CFS condition. At present there is also a sense of optimism amongst New Zealand researchers that the underlying cause could be viral in nature: Somehow, during the development of viral infection, the body's immune system has become dysfunctional and no longer copes with the body's daily exposure to pathogens and stress. An example is the reduction in regulatory T lymphocytes within the immune system. This reduction can affect the level of T suppressor (which reduces the production of lymphokines) as well as levels of T Helper Cells. The lowering of lymphokines reduces the level of

stress related to the symptoms of malaise, muscle pain and general discomfort following the immune systems response to pathogens. Shepherd (1989), has reported studies of subjects who were treated with interferon and others who were producing excessive interferon. In these studies, both groups produced more lymphokines and gradually developed some of the major symptoms of CFS, i.e. muscle fatigue and soreness.

1.06.B ENTERO VIRUS

The other group of virus that is suspected in the development of the CFS syndrome are pathogens that are harboured inside the alimentary system called enterovirus. The enteroviruses that live inside the gut system, but in particular the Coxsackie type, have been identified as present in the tissue of many CFS sufferers (Bell, et al 1988). The entero virus includes some deadly varieties that can attack the nervous system. The best known of these are the polio virus and the echoviruses that are responsible for the paralytic and often fatal diseases like meningitis (meningoencephalitis) [Merck Manual 1987]. To this day there are still no known cures for these viral infections. Fortunately, scientists have now developed specific tests that can identify parts of both the Coxsackie B and Epstein-Barr Virus (Holmes, 1991). Further more, studies of antibodies and lymphocyte

functions in patients with the Coxsackie B Virus have revealed deficits in both lymphocytes and the number of suppressor cells in the system of acutely ill CFS patients.

As previously discussed, immune deficits mean that people with CFS do not have adequate defence systems to combat microbial invasions of body tissue. The effort to ward off infection by the body's immune system is an on-going biological process involving a number of factors: The humoral immunity system producing immunoglobulin and the cellular immunity system producing specific lymphocytes like the B and T-lymphocytes. If these fail to materialize in the appropriate manner in response to foreign particles, the body system is likely to encounter biochemical stress as toxins from viral and bacterial cells develop within the body.

1.07 VIRUS AND CFS

Much of what is currently known about the role of viruses in CFS is still speculative. There is currently no hard evidence that viruses are causing muscle fatigue in CFS patients. Nor is it clear if they are responsible in any way for the triggering of pain or fatigue experienced by CFS sufferers. Never the less their presence in the body is today taken seriously enough for virologists to

continue investigations into their (viral) activities and possible physiological implications.

One recent speculation is that viral replication within host tissue may create physiological changes that are destructive of host organ and tissue development (Shepherd 1989). Viral units cannot reproduce on their own but are able to do so inside the host cell using the cells DNA mechanism. It is also now suspected that mutations by viral filaments within the host could also lead to basic changes within the autoimmune system. It is thought that this kind of change may arise directly from viral growth or from the bodies autoimmune mechanism reacting against the presence of virus. A number of modifications could happen as seen for example in the way retrovirus like the flu virus (found latent in CFS patients) will spread new infections after being dormant for months or even years (Holmes, 1991). One mechanism by which this event occurs lies in the ability of these microbes to infiltrate the genetic centre of the cell and effectively replicate together with the host cell when the latter is in the process of making new cells. This replication however, becomes more insidious when the cells being regenerated are the body's white cells, activated in response to the presence of pathogens in the body. In other words the spread of infection is accelerated when the body's immune system attempts to respond to the presence of a virus.

Not all investigators (Simpson 1991, Mukherjee et al, 1987, Lloyd et al, 1989) however, would agree that viruses alone could be responsible for all of the CFS condition.

1.08 VASCULAR INSUFFICIENCY

At the Prince of Wales - Prince Harry Hospital in Australia, there was speculation that gross abnormality in red blood cells made blood flow very difficult in the capillaries - thus creating a fatigue-like condition as seen in the case of long distance runners. This observation by Mukherjee (1985) was further developed by Simpson (1990) at Otago Medical School, who suggested that a discoid shape red cell problem was also a possible cause of muscle fatigue both in CFS sufferers and in other conditions like hepatitis. The hepatitis condition, according to Simpson,is characterised by the early appearance of a flu like illness that later develops into symptoms of physical and mental exhaustion in CFS patients. A check on patients, during the early stages of hepatitis, evidently reveals an increased number of non-discocytic erythrocytes in the blood (Simpson 1990). However, it is not known for sure if the fatigue experienced by ME sufferers relates to the shape or function of red cells in the blood . Simpson, nevertheless, is pursuing this matter in research in the hope of establishing a relationship between the experience

of fatigue and impairment of blood flow through body organs. Other scientists in New Zealand and USA suspect more obvious causes like the presence of parasites.

1.09 THE ROLE OF PARASITIC SPIROCHAETE

In 1975, an outbreak of an arthritic-like disease in children occurred in a small town of Lyme (Connecticut) in the USA. Examination of the problem revealed the cause to be the spirochaete Borrelia burgdorferi - a disease transmitted by ticks like Ixodes dammini found commonly on the coat of domestic pets. It is evidently possible for spirochaete' passed on by pets (cat, dog) to remain dormant in human body tissue and create an illness condition during its parasitic existence.

The spirochaete has been found in blood, spinal fluid, skin lesions (erythema chronicum migrans),inflamed synovia and other organs of the body. The symptoms are quite unusual. There is an onset of arthritic soreness in the joints which is associated with obliterative endarteritis and erosion of cartilage and sometimes bone. Then there is the characteristic development of the immune response system which is evident by the very high level of serum IgM in the blood. Further more , there is development of the more common symptoms of malaise, fatigue, fever and headaches with fatigue and malaise lasting several weeks

after the other symptoms have retracted.

In the USA, Lyme disease is the most commonly reported tickborne illness to affect both sexes and virtually all age groups - although there is a tendency to affect younger adults and children.

Snow (Otago Daily Times 1989) reported in a news article that the work being done in the USA to identify and deal with these microbes may reveal some causal mechanism for the development of ME. As he points out, spirochaete have a habit of infiltrating deeply into the host muscle tissue and remaining undetected for years but often only causing intermittent illnesses without showing up in blood or smear tests. It seems reasonable to suspect that the toxins released from these parasites will contribute to the feeling of sickness experienced by the host and could perhaps explain the muscle fatigue and feeling of weakness typical of ME symptoms. There might be a link between the incidence of CFS epidemics and prevalence of pet keepers in particular areas, but at the moment in New Zealand, this matter has not been considered very seriously.

1.10 CAN MINERAL DEFICITS MAKE SOME PEOPLE MORE SUSCEPTIBLE TO THE CFS SYNDROME ?

One issue that is being taken more seriously in New

Zealand with respect to CFS is the matter of mineral deficits.

Many CFS patients who are fortunate enough to be treated by their GP are usually put on a combination of mineral and vitamin supplements for several months if not years. This raises a number of important questions. Are there any health conditions affected by mineral deficits in New Zealand? Is CFS in any way caused by mineral deficits? Is there evidence that supplementation improves the well-being of CFS sufferers and how useful this type of therapy is in dealing with the CFS syndrome.

In New Zealand, as in Britain and parts of the USA, China and the Nordic countries, the very low level of certain minerals in the natural food source may lead to the speculation that some people may become susceptible to viral infections as a result of natural mineral deficits. It is known that certain mineral deficits can lead to specific pathological conditions. For example, iodine deficits can lead to cretinism, zinc to acrodermatitis enteropathica, Cobalt (Cyanocobalamin) to a compromise in myelin integrity (of neural tissue) and copper deficits to Menkes disease.

There are several anecdotal reports (MacIntyre 1990, Shepherd, 1989) that link viral infections (flu, sore

throat, swollen glands) with persistent feelings of illness when the virus concerned is not significantly eradicated. There are also reports that identify the persistence of illness feelings long after the patient had apparently recovered (Shepherd 1989). One implication of this finding is that the CFS syndrome may occur in people who have both with mineral deficits and have also suffered severe viral infections (e.g. the flu). The fact that the CFS sufferer seems to come from all walks of life (Lloyd, et al. 1990) might suggest, that the failure to recover quickly and completely from the condition may be due to a more basic health condition like mineral deficiency combined with a persistent viral infection.

In England, Cox et al. (1991) have suggested that the syndrome shown by ME subjects may be due to magnesium deficiency. Hypomagnesemia is a magnesium deficiency condition caused mainly through malabsorption within the renal system or alimentary tract as a result of illness conditions like diabetes or some form of thyroid anomaly (Merck 1987). Having low magnesium blood levels (<1.6 mEq/L) can lead to the development of complex nervous and muscular disorders similar to those seen in patients with serious hypocalcemia and hypokalemia. These disorders are also identified by symptoms (weakness, fatigue, muscle pain) similar to those seen in the CFS condition.

Cox et al investigated the possible importance of magnesium in a double blind, placebo/treatment trial with CFS and control subjects using intra-muscular magnesium injections. A pre-trial check on blood magnesium levels showed that CFS subjects were significantly lower in magnesium than the controls at the start of the trials. This study also found that CFS subjects were significantly improved in their feelings of well-being (using the Nottingham health profile). However, their blood magnesium levels increased with continued supplementation, as did their experience of well being during the course of the study.

Another example of metabolic disturbance and muscular problems, in this instance muscle wasting, as a result of mineral deficits is recognized in the condition of Keshan's Disease. Keshan's Disease (Robinson 1988), is an endemic disease characterized by the presence of cardiomyopathy, muscle fatigue and pain. The disease is significantly linked to a very low Selenium level in both food and body tissue (Passwater, 1980). Not surprisingly, successful treatment of this condition was achieved through Selenium supplementation (Thompson 1991). Further more this form of treatment once again stresses the importance of adequate mineral levels, but more important it high-lights the use of Selenium for maintaining good health. The problems of biological

disturbances arising from matters like vascular insufficiency, metabolic dysfunctions and mineral deficits are all likely to contribute to the general feeling of illness experienced by chronically ill patients including CFS sufferers.

1.11 SELENIUM AND HEALTH

The study of Selenium as an important mineral supplement has had many unexpected results. Although the precise role of selenium in any pathological condition is still not clearly understood (Thompson 1991), researchers have found that selenium's role in the anti-oxidant enzyme Glutathione peroxidase (GSHPx) is important in avoiding oxidation stress within cells (Thompson, et al 1987). Oxidation stress occurs when lipid peroxidation and the build up of hydrogen peroxide, during metabolism, develops to the point of oxidizing cell enzymes and breaking down other cell proteins. GSHPx is a selenocysteine molecule (containing four atoms of selenium) that stops lipid peroxidation and converts harmful hydrogen peroxide to water. Selenium may also act as an extracelluar oxidant or agent of transport (Burk, 1989) within the body tissues. Animal experiments (Combs and Combs 1986) have also indicated a possible protective role of high selenium levels in animal tissue against the development of tumorigenesis. (No one yet knows the mechanism by which

that protective function operates - some even doubt its existence). Epidemiological studies have likewise suggested a protective role of high selenium levels in humans against the development of cancer and possibly cardiovascular diseases (Thompson 1991). These functional aspects imply a reduction in physiological stress when the selenium levels are high enough to maintain adequate GSHPx levels. What is not understood is the so called 'adequate' level of selenium in the body. As Thompson (1991) recently pointed out, the problem of defining deficiency or toxicity with respect to selenium (or any other element for that matter) is still beyond our capability to measure in any scientific or meaningful way. So far, we know what can happen at the two extremes (deficiency and toxicity), but how much is needed for maintaining good health remains a mystery. In fact, at this point in time, nutritional science does not yet have any means of determining the optimal or minimal mineral requirements for proper nutritional status.

As already pointed out, so far we have little understanding about the role of the selenoenzyme GSHPx. But we do know that it does prevent oxidative damage arising from the build-up of peroxides in cells. Furthermore it is known that selenium does not operate on its own in cellular metabolism and Robinson lists a number of interacting factors including vitamins A, B, C, E and viral infections. An additional problem is the lack of

understanding about whether selenium plays a direct role in functional nutrition or is a limiting factor relating to enzyme activity.

Another interesting finding with selenium is its role in thyroid activity, as part of a selenocysteine containing enzyme (Berry, M et al 1991). Evidently, the active role of thyroxine depends on the presence of Type I iodothyronine deiodinase (a selenocystein-dependent enzyme) to convert T4 (Tetraiodothyronine) to T3 (Triiodothyronine) in the on-going process of growth and metabolism. Berry et al. (1991) have shown that, in rats, a deficiency in selenium will upset this process and inhibit thyroxine activity. Since thyroxine activity is linked to the active process of metabolism, it seems reasonable to expect general well-being to be improved when levels of selenocystein enzymes are raised.

One group of investigators (George and Walmsely - Princess Margaret Hospital) have recently postulated the possibility that lowering of thyroid activity (hypothyroidism) could increase hypercholesterolaemia (and possibly increase the chances of a heart condition). Part of the reasoning is based on the belief that people who generally experience more stress are also likely to develop eating disorders which may affect their level of thyroxine activity. People who suffer continual stress

are also likely to develop lower levels of wellbeing and may generally tend to put on more weight as a result of some physiological disorder associated with diet metabolism (George et al 1991). Again these people are thought to have lower levels of thyroxine activity which may cause higher levels of metabolic storage leading to serious weight gain and possible cardio-vascular problems Never-the-less, there is still no acknowledged medical condition currently in New Zealand that is related directly to deficiency in Selenium.

1.12 RELATED PROBLEMS IN MEDICAL CARE

A number of health issues seem to have no apparent explanation or reason and remain unresolved. The cot death rate in New Zealand is thought to be higher than in comparable western countries. The rate in Auckland is 2.5/1000 live births and is comparable to that in the USA, UK and Australia. But the rate in Dunedin and Invercargill is three times higher than in Auckland. Further more the daily intake of Selenium in Dunedin is much lower (< 30 mcg) than is the case in Auckland. In analysing the population blood selenium levels and distribution of cot deaths, Logan (1988 pp 190) has found a strong inverse correlation between the population diet selenium levels and the incidence of cot deaths (SIDS) in New Zealand. Evidently a similar finding has been

uncovered in Southern Australia and Tasmania (Logan 1987). Logan also points to the hypothesis of Money (1970) which suggested that selenium may be an important factor in the Sudden Infant Death Syndrome (Logan 1987).

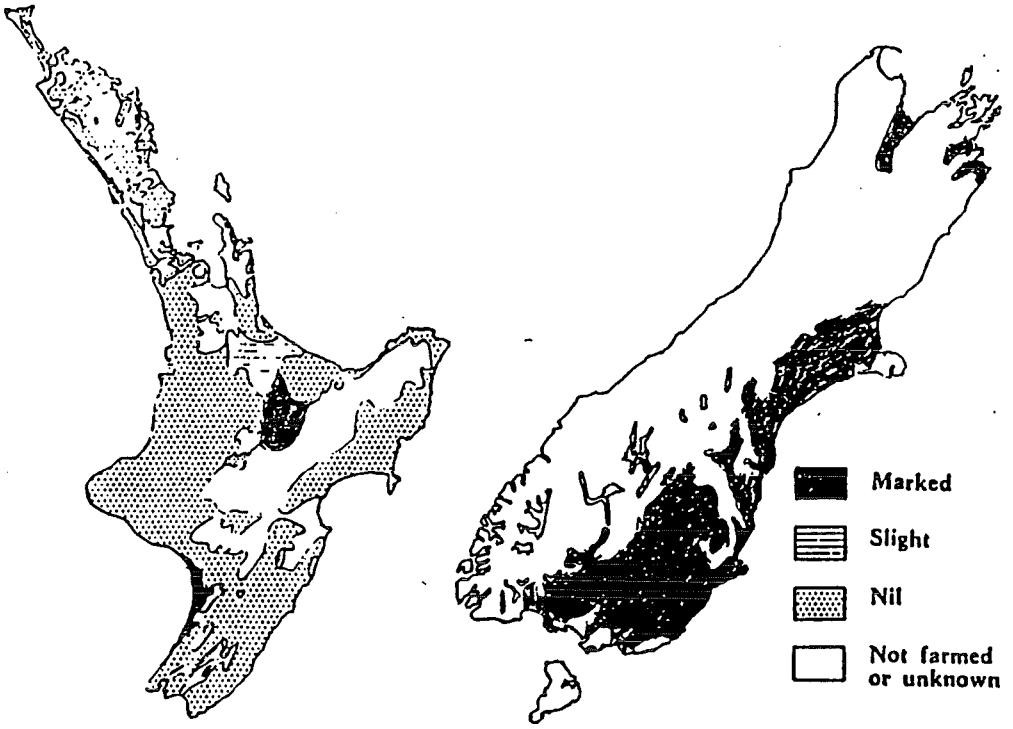
Despite the numerous anomalies and various unexplained health issues, Keshans' disease is not found in New Zealand. However, the major symptoms of CFS are myalgia and persistent fatigue. These symptoms would suggest a possible link between low Selenium levels and the general condition of CFS.

In the following section, we will discuss the scientific data relating to selenium and its possible effect on both the New Zealand population and other groups elsewhere in the world where low selenium levels are found.

1.13 SELENIUM IN NEW ZEALAND

Like many parts of Britain, New Zealand also has vast agricultural areas with low level selenium soils. Scientific reports as far back as the early 1960's (Watkinson 1962) have indicated a marked deficiency of selenium in New Zealand soil (Fig 1). This problem is accentuated in the South Island and in particular the East coast including most of the Otago region (DSIR 1965).

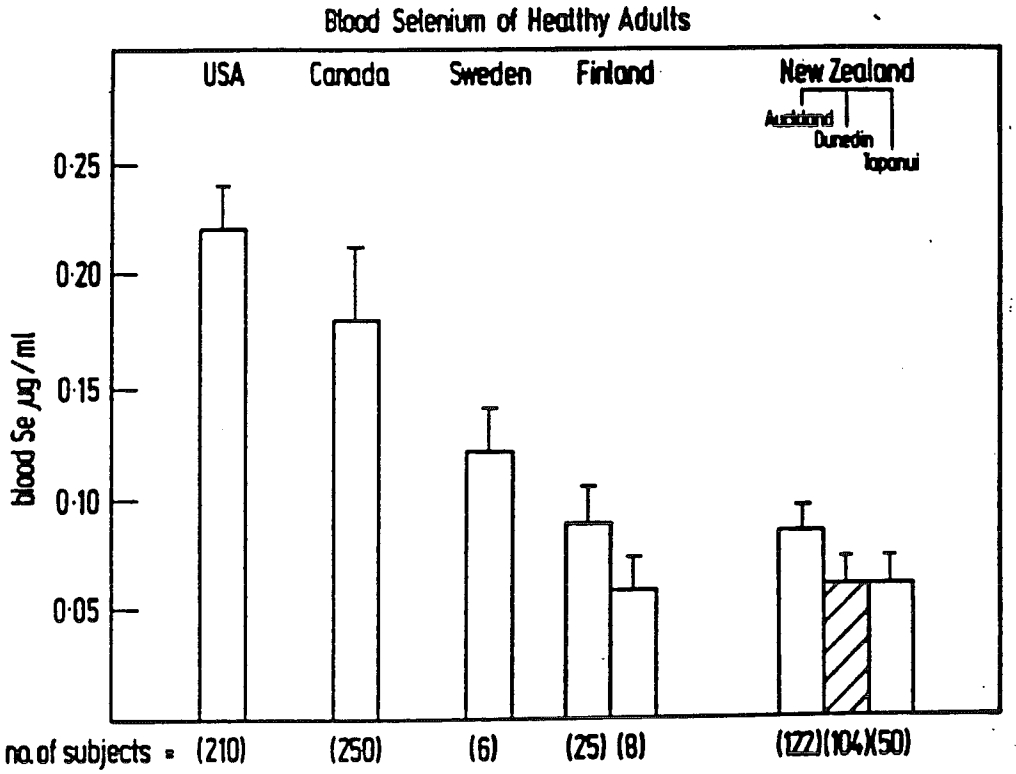
Fig. 1 MAP: THE MAIN SELENIUM DEFICIENT REGIONS OF N.Z



Source: Robinson - pg 14 "The moonstone"

According to Watkinson (1981), the New Zealand pattern of selenium deficiency seems to follow a north-south gradient where Aucklanders' selenium intake is higher than for those who live in Dunedin or Invercargill (see Fig 2 table). In the south-east parts of the South Island, residents are likely to have a selenium intake of less than 35mcg/daily (Thomson and Robinson 1974). Thompson and Robinson (1988) have also shown that locally grown and processed food reflects this low level (<0.05 mg/kg soil) of selenium. This low selenium content in the Otago region in particular, affects the food chain to the extent that food grown there provides less selenium for the food material used in human diet.

Fig 2. Table - Blood Selenium levels in healthy adults in 5 different countries



People in Otago experience a low selenium intake (25 mcg/d) from locally grown food resulting in low (< 0.01 mcg/ml) blood selenium levels (Thompson and Robinson 1988). Thompson also points out that but for the importation of Australian wheat, people in the North Island would also be experiencing low blood selenium levels.

Recently another report (Winterbourne et al 1992) has indicated an overall rise in blood Selenium, from 50 mcg/L - 90 mcg/L, (See fig.3) for the general population of Christchurch based on the increase of diet Selenium since the importation of higher Selenium wheat for the Canterbury flour mills from Australia; (the average Selenium content of blood in Christchurch New Zealand is between 40 and 50 mcg/L). Although the reason for the importation of wheat (See fig.4) is both commercial and political, there is no doubt that the health authorities are pleased with the trend and are hopeful of seeing an improvement in the general health of the public.

Fig 3. Changes in Plasma Selenium Found in Christchurch Adults in the Period from 1981 - 1992, (Winterbourne, 1992)

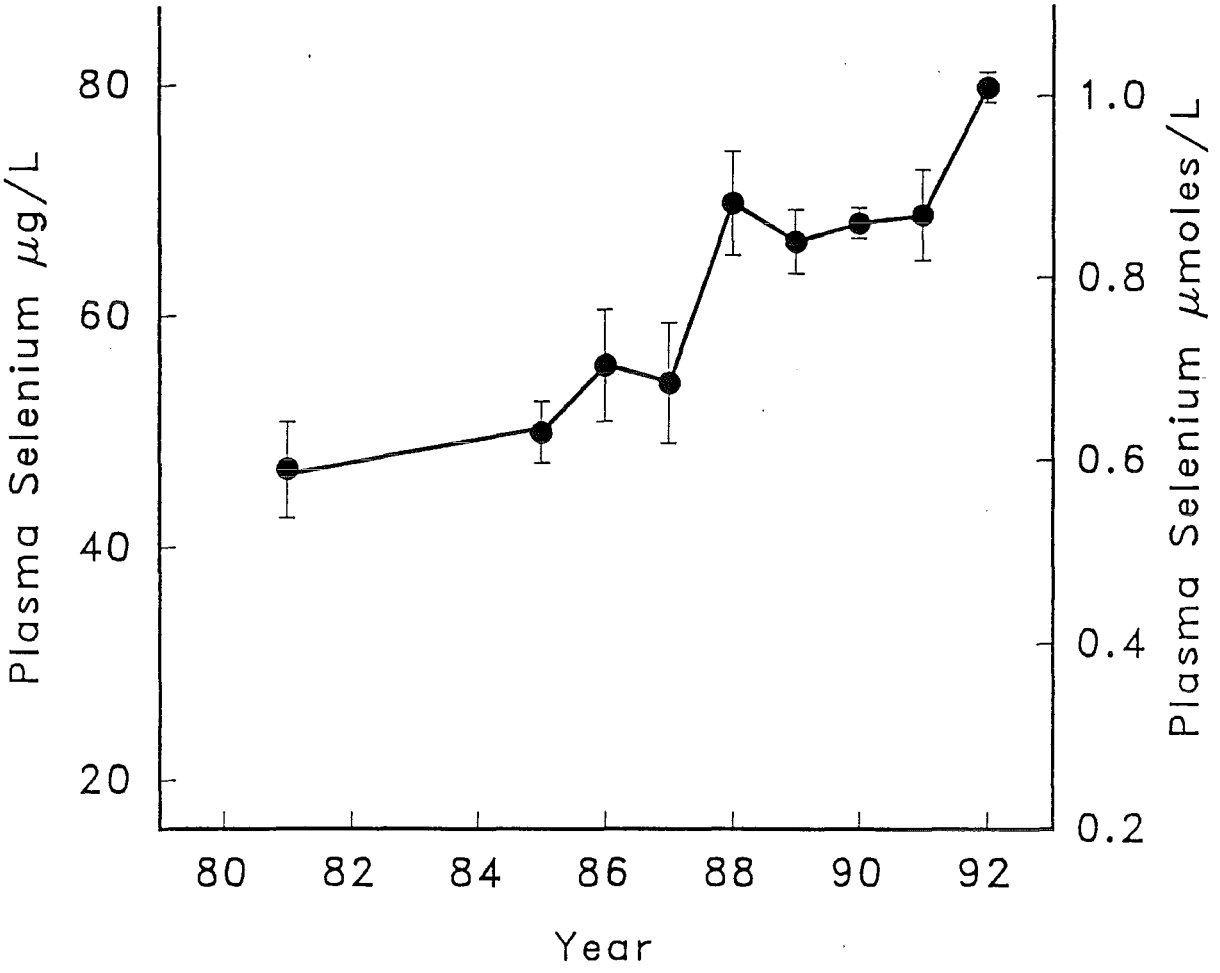
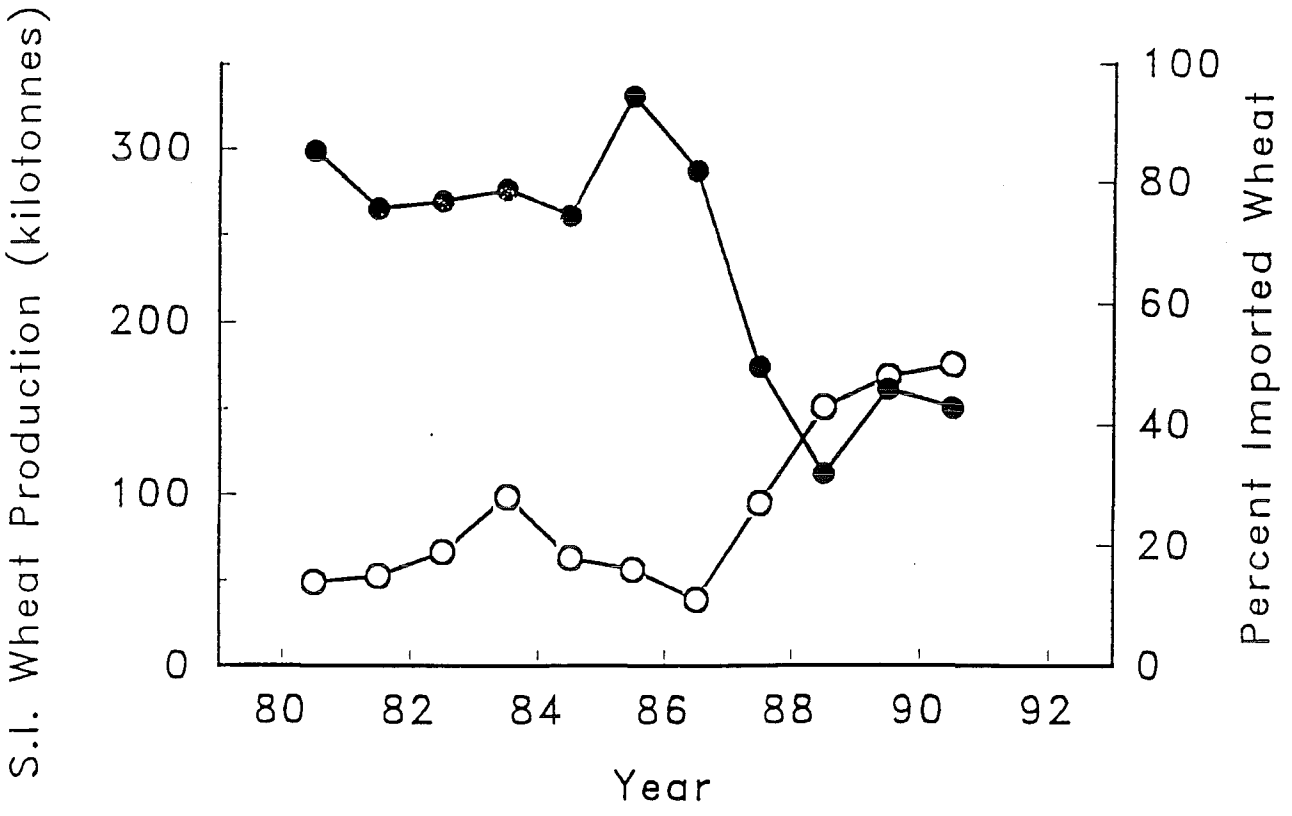


Fig. 4 South Island Wheat Production and Imported Wheat as a percentage of Total N.Z. Wheat, From 1981 - 1991 (Winterbourne, 1992)

Legend: o Total N.Z. Wheat Production



Tapanui, in south Otago, is a large rural region in the middle of a low soil selenium area in the South Island of New Zealand. Snow (1982), a GP in Tapanui, was the first to alert the health authorities on the development and increasing incidence of CFS (locally referred to as "Tapanui flu") in New Zealand. Through his concern for the unexplained suffering of many of his CFS patients, Snow was able to involve the medical research team in Dunedin (at the school of Medicine) to investigate the possibility of mineral deficiency and other matters relating to the plight of CFS sufferers. In the following discussion, we will examine closely the possible link between Selenium supplementation and feelings of well-being as shown in results from recent studies.

1.14 HEALTH, WELL-BEING AND SELENIUM - A STUDY OF EFFECT

It has already been pointed out that people who sometimes complain of being run-down and seemingly have no energy may be experiencing some kind of stress that may be related to or exacerbated by mineral deficits. It has been argued that selenium levels can affect thyroid activity which in turn can change our mood states (Berry et al 1991). In addition Passwater (1980), has argued that stress related to mineral toxicity arising from environmental pollution is decreased by the use of selenium supplementation. (Selenium is thought to replace

the more harmful minerals that can otherwise cause enzyme or protein destruction). The concern with low selenium levels in soil and food has been around for many years and some South Canterbury and Otago farmers have been known to consume the selenium product (sodium selenite) they use to drench their sheep and cattle (Trotter, B 1978, Robinson 1975).

A major health problem with stock in the south island is a collagen defect in muscle development called white muscle disease arising from insufficient selenium in stock food. White muscle disease causes stock to become lame and develop sores like those caused by infections. Furthermore, Watkinson (1962) had pointed out that sheep grazed on depleted soils with less than 0.5ppm selenium had a high incidence of selenium-responsive diseases. Many farmers in these selenium depleted regions believed their aches and pains were equivalent to the muscle problems of their stock (Trotter, B 1978). Further more they believed these symptoms would be alleviated by the use of selenium supplementation (Thompson 1991) in the same way that white muscle disease was overcome by selenium supplementation in animals. In 1981 Snow and others (Robinson et al 1981) at the School of Medicine (Otago University) reported a study that is particularly relevant to the present thesis.

The report was based on a study of the effect of selenium supplementation on subjects initially diagnosed as having painful experiences with fibromuscular rheumatism. This fatigue-like experience was one of the early symptoms later identified by Murdoch as typical of the CFS syndrome. The study involved different groups of patients in three separate trials over three different time spans (Tapanui-1974,Tapanui-1975,Tapanui-Christchurch-Gore-1977-1978) and involved what appeared to be separate groups of medical physicians in the different locations. Subjects for this study were selected on the basis that each presented the symptoms of muscular complaints (pain and fatigue) without any apparent cause that the examining physician could identify.

Treatment consisted of different levels and forms of selenium compounds (mineral selenite or organic selenomethionine) in varying durations. The three trials were identified as trial A ,B and C (1974, 1975 and 1977-1978 respectively).

In trial A, 20 patients fitting the clinical criteria of having muscular complaints, as in fibromuscular rheumatism, were given a daily dose of 500 mcg sodium selenite in liquid form for twenty days.

In trial B, 24 patients (10-60 yrs) fitting the same

criteria were selected for testing. Twelve were given a 5 ml solution of semet-selenium (organic selenomethionine) and the other 12 a 5 ml placebo for 12 weeks on a double - blind trial. Selenium blood tests on all patients were carried out before taking treatment and then every two weeks thereafter. A final blood test was carried out 8 weeks after the final dosing to determine any significant changes.

In trial C 78 patients (29 from Tapanui, 37 from Christchurch, 12 from Gore) were given a capsule of 90mcg selenite selenium mixed with 20/10 vitamin E or a placebo in a double blind trial.

Assessment of each of the above treatment was made in two ways. The objective method required the physician to record signs (or lack of them) of improvement in symptoms that were diagnosed earlier in each subject. The subjective technique relied on physician and patient both rating the level of improvement as they felt at the time of interview, using a 0 - 3 four point rating scale (0 being complete resolution of all symptoms and 3 = no improvement or worsening of symptoms).

Using the above criteria, collected data from trial A showed ten subjects had improved and ten did not. In trial B, the overall result of the clinical assessment of

symptoms indicated 11 had recovered and 12 were unchanged. In trial C, again no significant difference between the group on placebo and the group on selenium could be found (38 recovered, 39 did not). In all three trials, subjects on selenium showed a significant increase in blood selenium levels compared to those on Placebo. However, there are problems raised about the efficacy and validity of certain aspects of the study.

Although the aim was to investigate the alleged beneficial effect of selenium supplementation (reported by some farmers), there was no attempt to examine the psychological profile of patients who complained of the unexplained muscle pain and fatigue. It is difficult to see how the impact of treatment could be measured effectively if the assessment was limited to a criteria of observing symptoms (muscular) being present or absent at the time of interview using a relatively crude rating scale that concentrates only on "muscle weakness". The evaluation was also carried out by multiple examiners for separate groups.

Hence the issue of varying levels of body selenium and the effect that might have on mood levels of CFS subjects is one that still needs to be carefully investigated. To understand how subjects with CFS are affected requires a knowledge of their mood profiles and the way their mood might change in relation to blood selenium levels.

1.15 SELENIUM AND MOOD CHANGE

Benton and Cook (1990) in Wales have also noted that there were low levels of selenium in both food and soil in Britain. What was equally important was the trend towards a lowering of this level in England due to a greater reliance on locally grown products rather than imported wheat from Canada with its much higher selenium content. This being the case, Benton points out that an average intake of 43 mcg/day in Britain is well below the recommended level of 50-200 mcg for adults. The possibility of health in general being affected by this low level was examined in the following investigation.

1.16 THE BENTON/COOK SELENIUM INVESTIGATION AND THE PRESENT STUDY

Benton and Cook (1990) investigated the role of selenium supplementation on the mood states of a university population living in Wales (UK). In this study 17 males and 33 females (age 22-54) were given 100 mcg of selenium or the yeast placebo supplement in the form of a tablet taken once a day for five weeks, using a double-blind, cross-over design.

Before the treatment began, at week 2.5, and at the end of week 5, all subjects were given the Bi-Polar Profile Of

Mood StateS (POMS, Lorr and McNair, 1982) questionnaire to complete. At the end of the first five week period, subjects were put on a six month wash out tablet-free period. At the beginning of the second five week period, subjects' mood was again reassessed and each subject given the alternate tablet for the second five week period. The results indicated that selenium supplementation was responsible for increasing mood scores. Subjects on placebo did not show any significant change in their mood score. The conclusion was that mood scores improved over time when selenium (rather than placebo) was taken by subjects.

In a subsequent follow up study Benton and Cook (1991) further concluded that selenium deficiency in the British diet is closely related to lower levels of well being and that raising selenium intake promotes a higher level of well being for their subjects. In this investigation (Benton and Cook 1991), the food intake of all subjects was monitored by way of interviews and food frequency questionnaires. From this information they selected subjects who were on "high" as opposed to "low" levels of selenium food intake. When given selenium supplementation, subjects on low diet selenium showed a significant increase in mood score. But more important, subjects with low dietary selenium showed a more significant increase in mood score. This means that

people with low selenium intake may have a greater need for selenium. It is clear from Benton and Cook that selenium has a role to play in the mood levels and possibly the experience of well being in subjects. How selenium affects mood is not clear. But one interesting speculation relating to iodothyronine (Berry et al 1991) was discussed earlier on. Never the less it is a well known fact that hypothyroidism is characterised by symptoms of mood apathy and retarded speech (Rosenzweig and Leiman 1989, Merck 1987). In more severe iodine deprivation, the syndrome called Myxoedema begins to emerge and the symptoms of fatigue, weakness, aching muscles and cramps become more prevalent (Houston et al - A Short Textbook of Medicine 1968). But obviously, and from Benton and Cooks'(1990,1991) results, mood elevation can be linked to selenium supplementation and if that is true, then perhaps the converse (low selenium) might be a partial explanation for having lower mood levels. The diagnosis of depressive mood levels in CFS sufferers is a common feature of the CFS syndrome.

In the current study, it is also speculated that selenium may play some part in controlling mood changes in CFS subjects. The present study, therefore, but in the context of another (i.e 'healthy' New Zealanders) population, attempted to replicate in part the Benton and Cook (1991) study and further more to examine the question

of whether selenium supplementation may also have an effect on subjects who have been diagnosed as CFS sufferers.

From the foregone discussion it should be clear that the major question for the present thesis is the effect of selenium supplementation on the well-being of those suffering from CFS and a healthy comparison control. In this study, the main aim was to examine carefully the effect of selenium supplementation on both CFS and non-CFS subjects. But we were also interested in the relative differences between the two groups of subjects and in particular whether the normal controls could reflect the impact of selenium on mood as was shown by Benton and Cook in their investigation.

Chapter 2 METHODS

2.1 SUBJECTS

Only CFS subjects diagnosed by Professor Murdoch, using the criteria listed pp 5, were considered for the CFS group in this study. Furthermore, we excluded those who had other illness conditions or may have suffered any Non-CFS neurological, psychiatric or psychological disturbances (see table - appendix). The controls were selected on the basis that they were free of any past or present major medical or psychiatric illness condition.

In total, thirtyseven CFS subjects (8 males, 29 females) invited took part in a placebo controlled study. Each CFS subject was matched (age, sex, socio-economic status and ethnic origin) with a healthy non-CFS control. The age range was 23-55. (see Fig. 5 and 6).

Fig. 5

Group: mean age and standard deviation

GROUP X TREATMENT	Mean Age	S.D
Healthy Controls/ placebo	37	11
Healthy Controls/ selenium	39	10
CFS/ placebo	37	11
CFS/ selenium	40	10

Fig. 6

Group Size

GROUP	TREATMENT	SAMPLE SIZE
Healthy Controls	Placebo	18
Healthy Controls	Selenium	19
CFS	Placebo	14
CFS	Selenium	19

Each matched pair was randomly assigned to one of two treatment (selenium / placebo) groups and given the same treatment throughout. A few subjects who initially started in the study withdrew for a variety of reasons. Three controls found the study requirements too difficult to adhere to. Two CFS subjects became too ill to continue. One CFS subject who felt well on the treatment (i.e reduced muscular pain and arthritic inflammation) found she was experiencing a 'high' she could not cope with. A week after she refrained from taking the tablet (which incidently was selenium) she reported feeling 'normal' again - and was much happier for it.

In the final analysis, thirty three CFS subjects and thirty seven controls completed the trial.

The selection of subjects was carried out during the late summer period (January-February 1991). A noticeable feature of the CFS group, was the high incidence of unemployment, perhaps a testimony to the severity of the syndrome (and economic stress) in the Otago-South Canterbury region of New Zealand.

All subjects who took part in this study were personally interviewed by the present author and each gave informed, written consent and was made aware of their

right to withdraw at any time they felt it necessary. During the interview an overview of the whole programme was outlined including what was required of each subject. An information sheet containing this summary was given to each prospective subject.(see appendix). Ethical approval for the present study was obtained from the Canterbury and Otago Area Health Boards, and the Human Research Ethics Committee of the Department of Psychology at Canterbury University .

2.2 TREATMENT PROTOCOL

Treatment comprised of a selenium tablet containing 150 mcg of selenium (as selenomethionine) in a yeast-free base, or an appropriate neutral placebo that had no selenium (supplied by Vitafit Megavitamin laboratories-Christchurch). The chosen level of 150 mcg selenium was based on the literature (Robinson 1988, Thompson 1991, Spallholz 1989) suggesting that levels of supplementation between 100 and 200 mcg would be sufficient to effect an increase in blood selenium levels of treated subjects. Our six week trial period also had sufficient duration for the body to adapt and adjust to the increase in selenium treatment.

Subjects were matched and paired and each pair was randomly allocated to a treatment condition (Selenium or

placebo) such that each CFS subject and the corresponding Non-CFS control were subject to the same treatment condition at the same time.

We were careful not to employ any material in the treatment (or placebo) that may exacerbate the symptoms of our CFS volunteers. One important aspect of the CFS condition is the sensitivity of many of these subjects to yeast, cereals and dairy products. Hence, both tablets were made from cellulose with the minimum of calcium and magnesium binder added to create a homogeneous form that would make one tablet indistinguishable from the other. Subjects were also advised that should a tablet be forgotten on one day that a maximum of two should be taken the following day. To help subjects and as a memory aid , each was also given a specially designed wall calender that actually indicated the start, finish, blood testing and mood testing dates of the trials, plus a calender for checking whether the daily tablet had been taken, was affixed to the tablet bottle.

Subjects who were willing to do so, presented themselves for a blood test that involved the removal of a 5-10 ml sample of blood. The blood tests were done just prior to the commencement of the treatment trial and immediately following the conclusion of the sixth week

(All blood samples were collected in a hospital or a medical laboratory). Subjects were informed that a blood test was not critical to ongoing participation in the trials although it was pointed out that we did require some blood checks to verify the pre and post trial selenium levels of subjects in general.

The taking of blood samples from subjects was done by experienced medical staff at the Hospital Laboratories in Dunedin, Oamaru, Timaru and Princess Margaret Hospital in Christchurch. Biochemical analysis of plasma selenium was performed by Mr Walmsley at the Biochemistry Department of Princess Margaret Hospital using a standardised carbon furnace spectrophotometer procedure developed at Christchurch Hospital. Plasma selenium is regarded as an effective measure of changes in selenium status (Thompson 1991). About two thirds of all subjects underwent blood tests both at the pre and post trial periods of the six week trial.

2.3 EVALUATION PROTOCOL

Subjects mood changes were measured by two sets of questionnaires. These were the Beck Depression Inventory- BDI, (Beck and Steer, 1987), and the Profile Of Mood States (POMS)- Bi polar form (Lorr and McNair,1982) Each set was completed just before the

tablets were started, at the end of week three, and at the end of the sixth week of the trial.

At each testing, subjects were in small groups of from 10 to 15. (depending on location). On each occasion, subjects were given the POMS followed by the BDI. In each case a set of instructions for each questionnaire was read to the group detailing the way that particular questionnaire should be answered. Subjects were then advised to read carefully the instructions on the front of the questionnaire and to ask any questions about matters they were still unclear about. One major problem that some subjects had difficulty with was the ability to conjure up an average perception of the past week and then be able to rate it according to the immediate question. It was explained that the main point was how they perceived of the week as a whole rather than just one day that may have been stressful or pleasant. When these matters were sorted out to the satisfaction of all concerned, the group were asked to start. Some specific instructions for each test are outlined in the following description of the two questionnaires.

(Sample questionnaires can be found in the index)

2.4 BECK DEPRESSION INVENTORY (BDI)

The BDI was scored by adding up the 21 ratings (0-3) made by subjects. The score range is 0-63. A high score would indicate a severe level of depression. A few subjects found the language difficult and had to concentrate to get through the questionnaire.

2.5 PROFILE OF MOOD STATES (POMS; BI-POLAR) - 1980 EDITIONS

The use of this questionnaire followed the guide lines provided by the manual. The questionnaire consists of 72 adjectives describing feelings and different moods. Subjects indicate how they have been feeling over the past week by ticking a point on the four point scale - much unlike this; slightly unlike this; slightly like this; much like this. McNair et al (1971) have suggested a total mood score can be calculated so that those with a high score are composed rather than anxious, agreeable rather than hostile, elated rather than depressed, confident rather than unsure, energetic rather than tired and finally clearheaded rather than confused.

Each of the adjective pairs reflects one of the six component bipolar mood states measured by twelve of the adjective check list of 72 adjectives.

2.6 DATA ANALYSIS

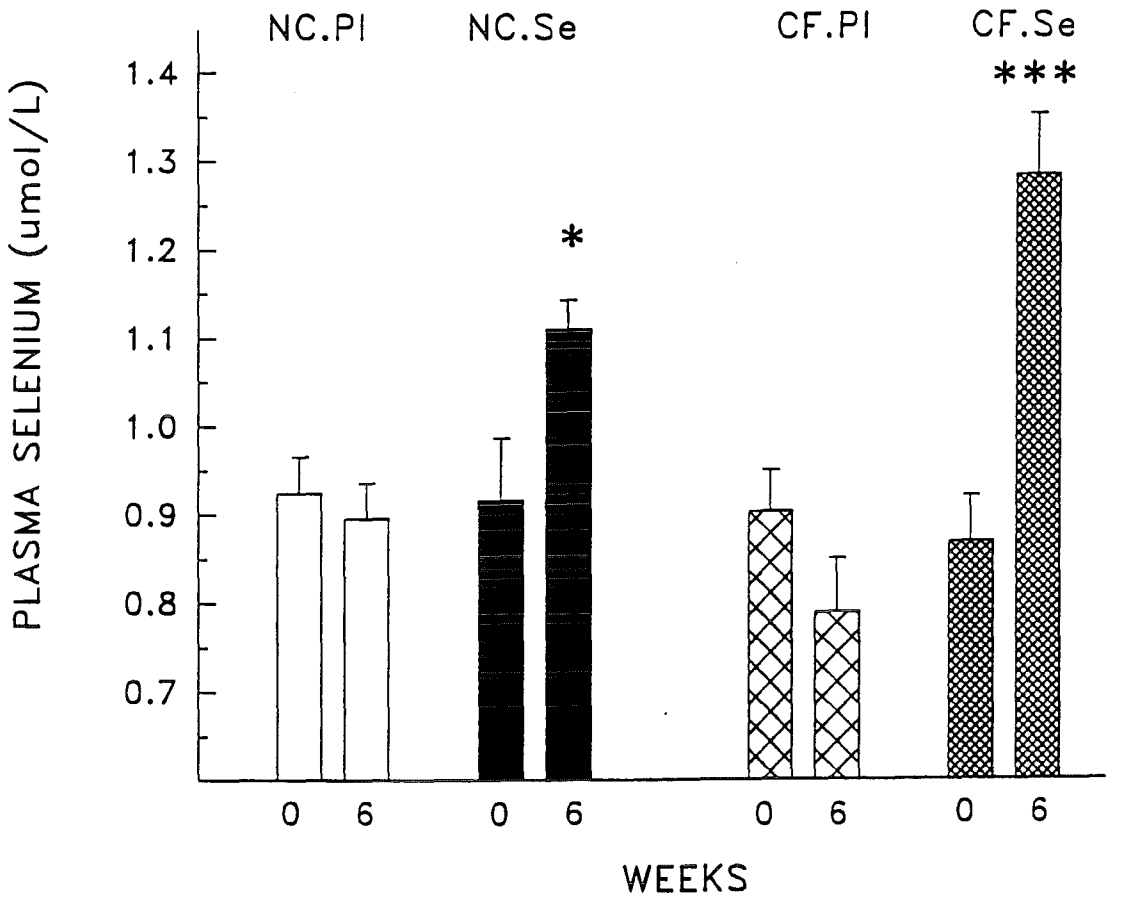
Total mood scores from the three questionnaires were subjected to an analysis of variance with Group (CFS vs Non-CFS) and Treatment (selenium vs placebo) as the two between subject factors and Time (0vs3vs6 Weeks) as the repeated measures. The six subscores from the POMS and the BDI scores were also subjected to a similar analysis of variance. A two level repeated measure for time (0vs6 Week) was used for the Blood selenium data. These univariate analyses were carried out using a general Manova package (CSS;Statsoft).

Chapter 3 RESULTS

3.01 BLOOD SELENIUM LEVELS

The results from blood tests (Fig 7) revealed that blood selenium levels in both groups of subjects was generally low, as expected (Robinson 1988). However, they also showed that the low selenium levels in CFS subjects were not significantly different from the low levels in their Control counter-parts at the start of the supplementation trial ($F<1.0$). Blood Selenium levels showed a significant increase following supplementation (Treatment (Selenium vs Placebo) X Time interaction, $F=27.74, df=1,44, P<0.0001$) and there was a significant interaction between Group (CFS vs Controls) x Treatment x Time ($F=4.66$, $df=1,44$, $P<0.05$). When we examine each group separately, there was a Group X Treatment interaction for controls ($F=4.49; df=1,44; P<0.05$), but a much clearer increase in blood selenium levels was evident in the CFS group (Treatment X Time, $F=29.82; df=1,44; P<0.0001$). Thus CFS subjects appeared to respond to Selenium supplementation more than did the Controls (Group X Time interaction for selenium treated subjects, $F=4.98; df=1,44; P<0.05$).

Fig. 7 Plasma Selenium Levels Measured in Both CFS and Control Subjects

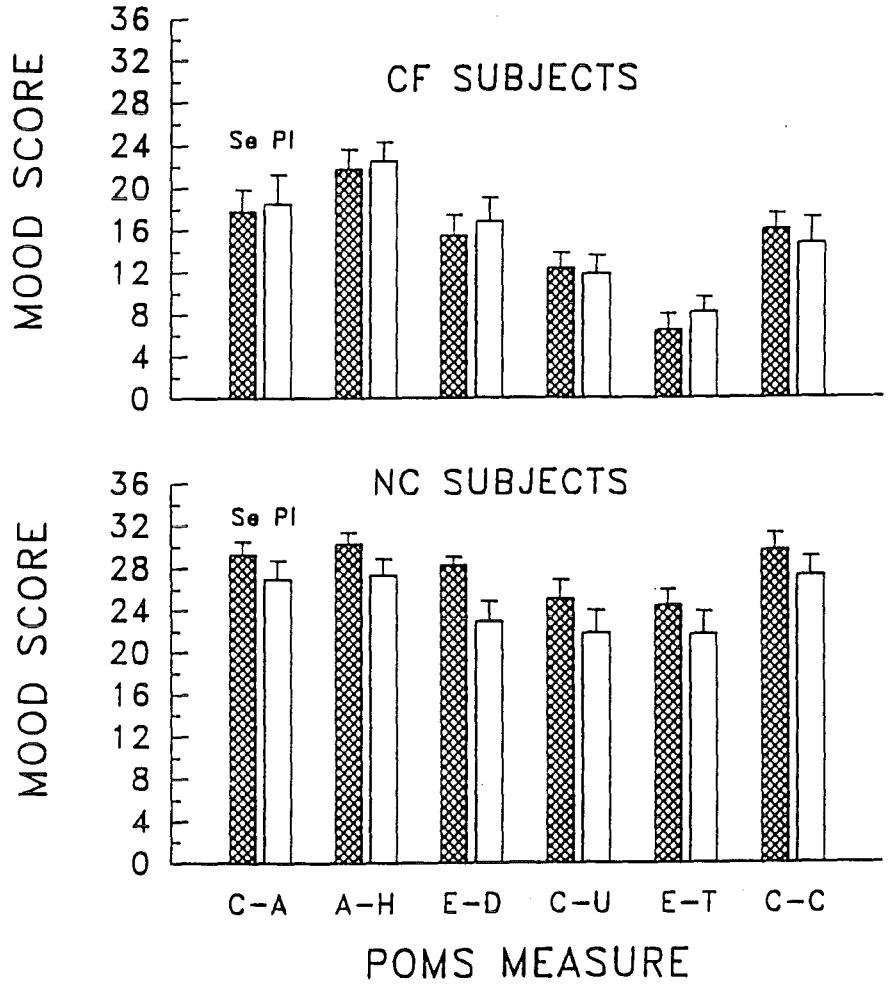


3.02 PROFILE OF MOOD SCORES FOR CFS AND CONTROL SUBJECTS

The profile of mood states for the two groups at the beginning of the trial (0 week) is shown in figure 8. These 6 measures were subjected to a 2(CFS vs Control) x 2(Selenium vs Placebo) X repeated measure of 6 component mood scores. The mean total mood score for CFS subjects was considerably lower the than mean total mood score for Control subjects (Group main effect, $F=60.75;df=1,66;P<0.0001$). However, there was no difference between subjects who were to be given selenium as opposed to placebo (Treatment effect, $F<1.0$; Group x Treatment interaction, $F=1.6;df=1,66;P>0.10$).

There was a significant main effect of mood measure ($F=40.44;df=5,330;P<0.0001$). However, the profile of mood scores was different between the two groups as shown by the highly significant Group X Component mood score interaction ($F=7.19;df=5,330;P<0.0001$). For Control subjects the measure of composed-anxious,agreeable-hostile and clearheaded-confused were equal but were higher than elated-depressed, which was greater than confident-unsure and energetic-tired measures; the latter were similar. In contrast, the measure of agreeable-hostile was higher than all other measures whereas energetic-tired was by far the lowest, even relative to the confident-unsure measure.

Fig. 8 The Profile of Mood Scores for the CFS and Control Subjects



3.03 EFFECT OF SELENIUM ON TOTAL MOOD SCORE

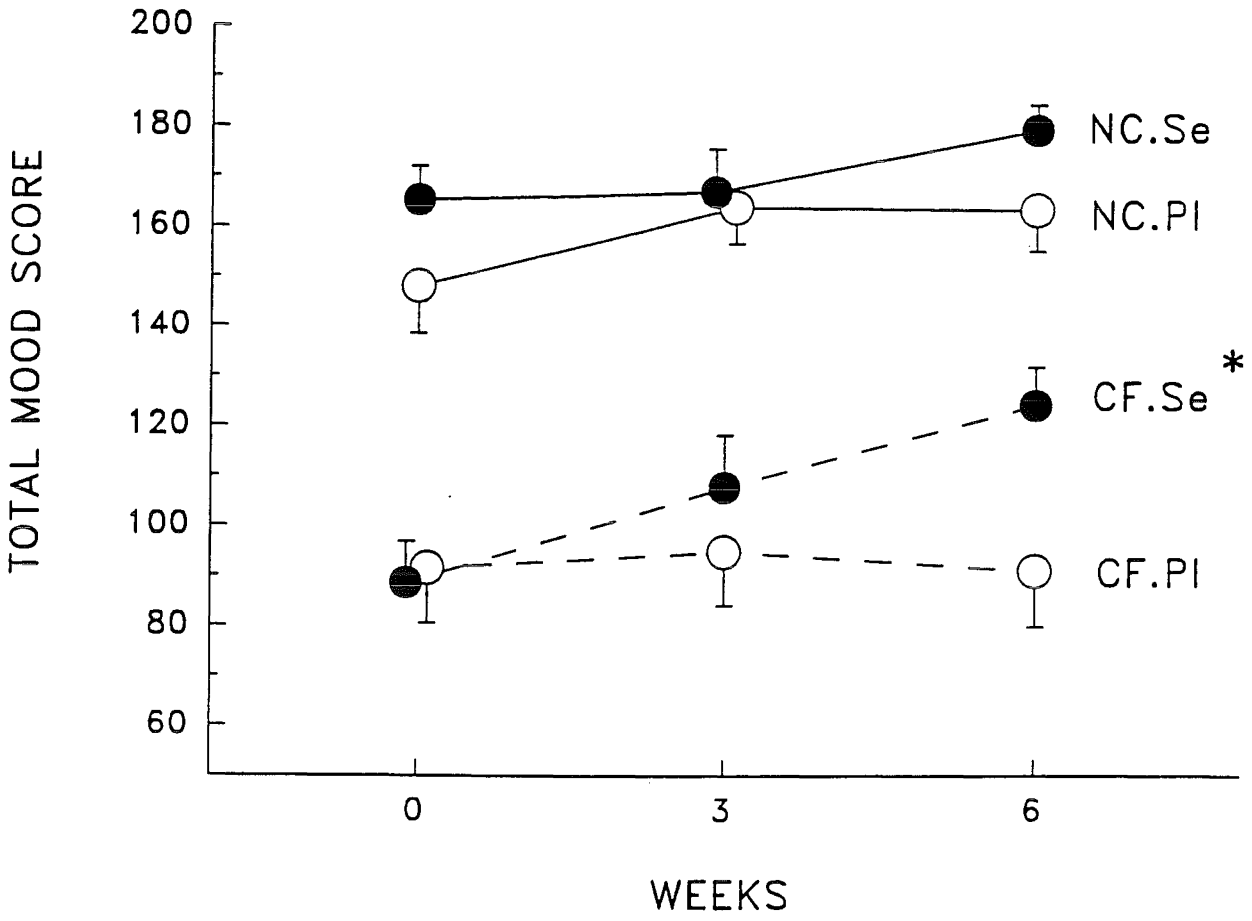
Fig. 9 shows total mood scores for CFS and Control subjects given Selenium or Placebo in the 6-week trial. The total mood scores for the two control sub-groups are higher than the mood scores for both CFS sub-groups (main effect for Group, $F=84.70;df=1,66;P<0.0001$). The main effect of Treatment (selenium vs placebo) just failed to reach significance ($F=3.49;df=1,66;P<0.06$). However, the difference in total mood scores over time for the two groups is significant (main effect of Time,$F=6.43;df=2,132;P<0.01$). There were no significant interactions for Group x Treatment or Group X Time, but there was a suggestion of an interaction for Treatment X Time ($F=2.37;df=2,132;P<0.10$) and, more importantly, there was also a suggestion of an interaction for Group(CFS vs Control) X Treatment (Selenium vs Placebo) X Time ($F=2.45;df=2,132;P<0.10$).

Given the suggestion of this three way interaction, a planned comparison of the Treatment by Time interaction for the CFS group and the control group separately was carried out. These analyses revealed that the Treatment by Time interaction for control alone was not significant ($F<1.0$) but, by contrast, there was a significant Treatment by Time interaction ($F=3.81;df=2,132 ;P<0.05$) for the CFS group. The simple main effect of Time for

CFS/Placebo sub-group was not significant ($F<1.0$) whereas the simple main effect of Time for the CFS sub-group taking selenium was highly significant ($F=8.64;df=2,132;P<0.001$). In addition, the increase in total mood scores in CFS/Selenium subjects was statistically significant between both 0 week vs 3 week test($F=4.40;df=1,66;P<0.05$) and 3 week vs 6 week test ($F=4.55;df=1,66;P<0.05$), and total mood scores of CFS subjects on Se were different from the total mood scores of their CFS counterparts on placebo at week 6 (simple main effect of treatment at week 6, $F=7.96;df=1,66;P<0.01$). weeks).

An examination of the individual scores in the CFS/Se group revealed that 16 of the 19 CFS/Se subjects improved their total mood scores during Se treatment. Twelve of these subjects reached a score of 140 or better by week 6. This means 64% of CFS subjects on Se treatment showed an improvement that saw their mood levels elevated to the same pre-treatment level shown by controls.

Fig. 9 Total Mood Scores For Both CFS and Control Groups



3.04 COMPOSED-ANXIOUS SCORES

These data are shown in Fig. 10. CFS subjects had a lower score on this measure (main effect of Group, $F=50.17;df=1,66;P<0.0001$). There was also a treatment main effect, subjects on selenium scored higher than on placebo ($F=3.91;df=1,66;P<0.05$). No other effects approached significance except the Treatment X Time interaction ($F=2.31;df=1,132;P<0.10$). The placebo groups did not change over time, but there was an indication that selenium groups improved over time ($F=3.54;df=2,132;P<0.05$).

3.05 AGREEABLE-HOSTILE SCORES

These data are shown in Fig. 11. The only significant difference to emerge was a Group main effect ($F=26.72;df=1,66;P<0.0001$) and a Time main effect ($F=3.29;df=2,132;P<0.05$). No other effects approached significance.

Fig. 10 The Composed - Anxious Subscores for CFS and Control

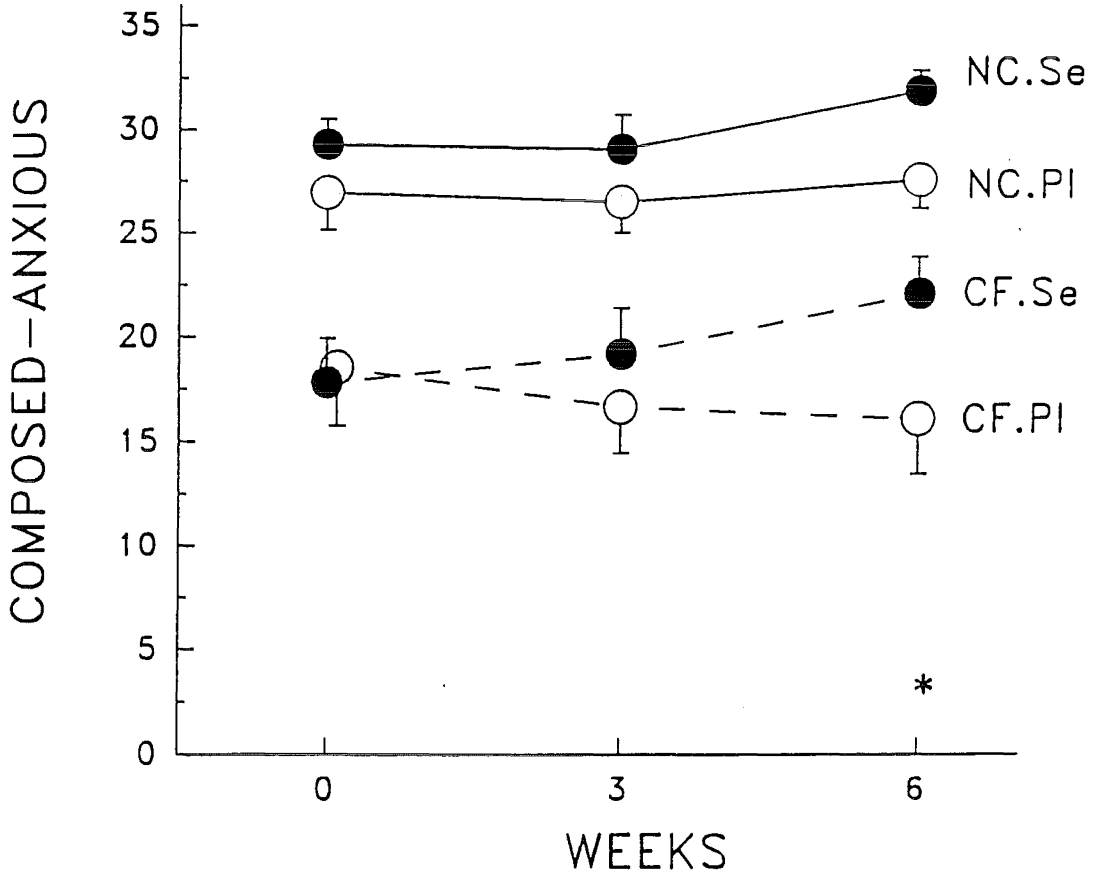
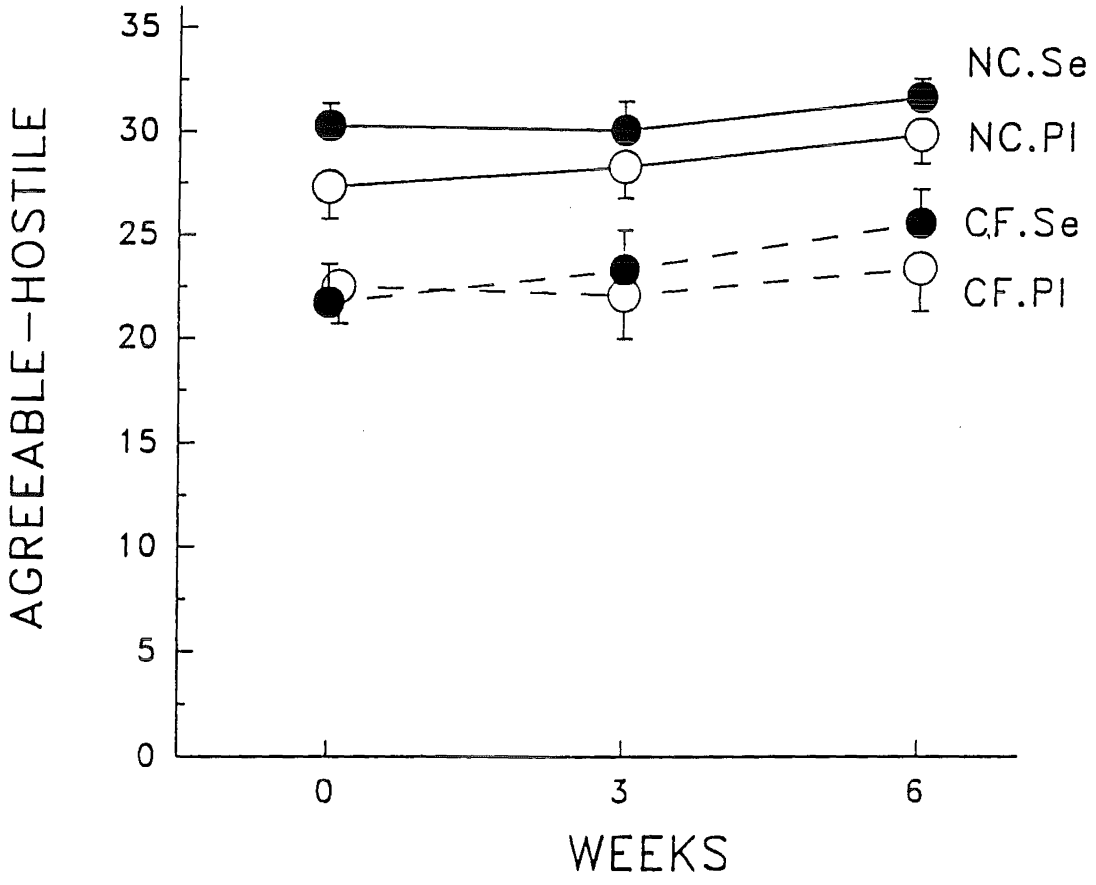


Fig. 11 The Agreeable - Hostile Subscores for CFS and Control



3.06 ELATED-DEPRESSED SCORES

These data are shown in Fig. 12. There was a significant Group main effect ($F=53.98;df=1,66;P<0.0001$) and a significant Time effect ($F=5.93;df=1,66;P<0.01$) but the main effect for Treatment failed to reach significance ($F=3.33;df=1,66;P<0.1$). The Group X Treatment X Time interaction was significant ($F=4.02;df=2,132;P<0.02$). As shown on graph, the selenium/control group was higher than the placebo/control group at 0 weeks, but the CFS/Selenium group was higher than the CFS/placebo at 6 weeks. However, the Treatment X Time interaction for the CFS groups did not reach significance($F=2.68;df=2;P<0.07$).

3.07 CONFIDENT-UNSURE SCORE

These data are shown in Fig. 13. The only notable effects were that CFS scored much lower than controls ($F=66.45;df=1,66;P<0.0001$) and a highly significant increase in scores over Time($F=8.64;df=2,132;P<0.001$).

Fig. 12 The Elated - Depressed Subscores for CFS and Control

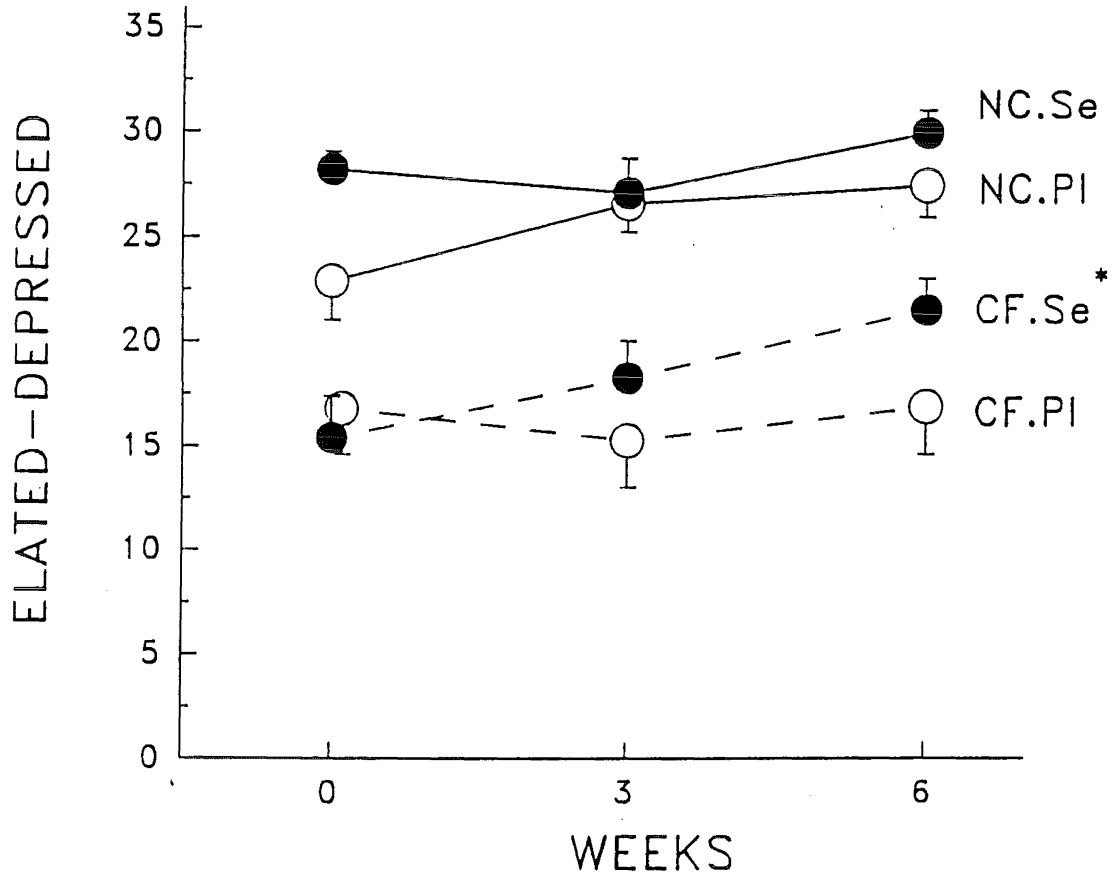
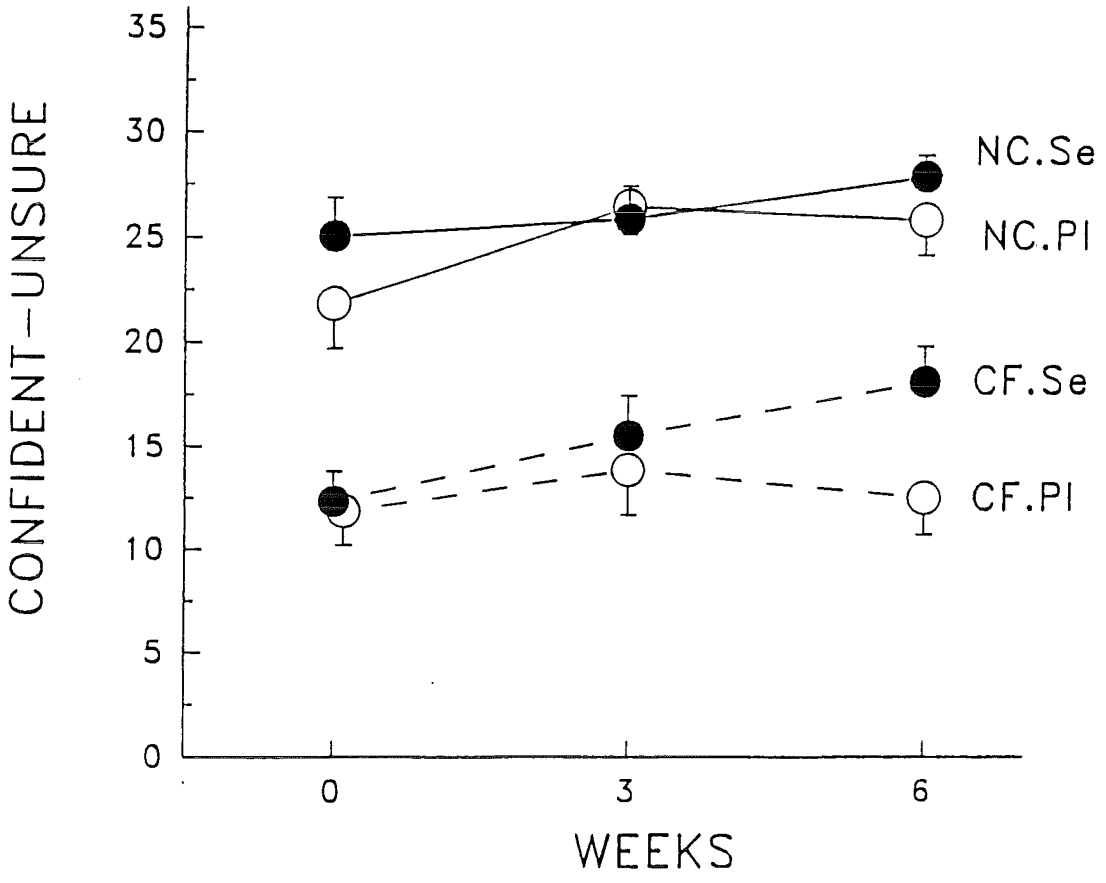


Fig. 13 The Confident - Unsure Subscore for CFS and Control



3.08 ENERGETIC-TIRED SCORE

These data are shown in Fig. 14. There was a significant main effect for Group ($F=145.96;df=1,66;P<0.0001$), no main effect of Treatment ($F=2.23$; $df=1,66$; $P>0.10$) and an increase in score over Time ($F=5.91;df=2,132;P<0.01$). However, there was also a Treatment X Time interaction ($F=4.08;df=2,132;P<0.02$). Analysis of the simple main effects of this interaction showed an increase in mood score in the selenium Group only ($P<0.01$).

3.09 CLEARHEADED-CONFUSED SCORE

These data are shown in Fig. 15. There is a main effect for Group($F=60.03;df=1,66;P<0.0001$), a main effect for Time ($F=3.95;df=1,132;P<0.05$) but the main effect for Treatment was not significant ($F=3.35;df=1,66;P<0.07$). There was an indication of a Group X Time X Treatment interaction($F=2.44;df=2,132;P<0.10$). There was no Treatment X Time interaction for controls($F<1.0$) but there was one for CFS subjects ($F=3.97;df=2,132;P<0.05$). Selenium CFS subjects showed a highly significant increase in mood scores over Time($F=8.69;df=1,132;P<0.001$).

Fig. 14 The Energetic - Tired Subscores for CFS and Control

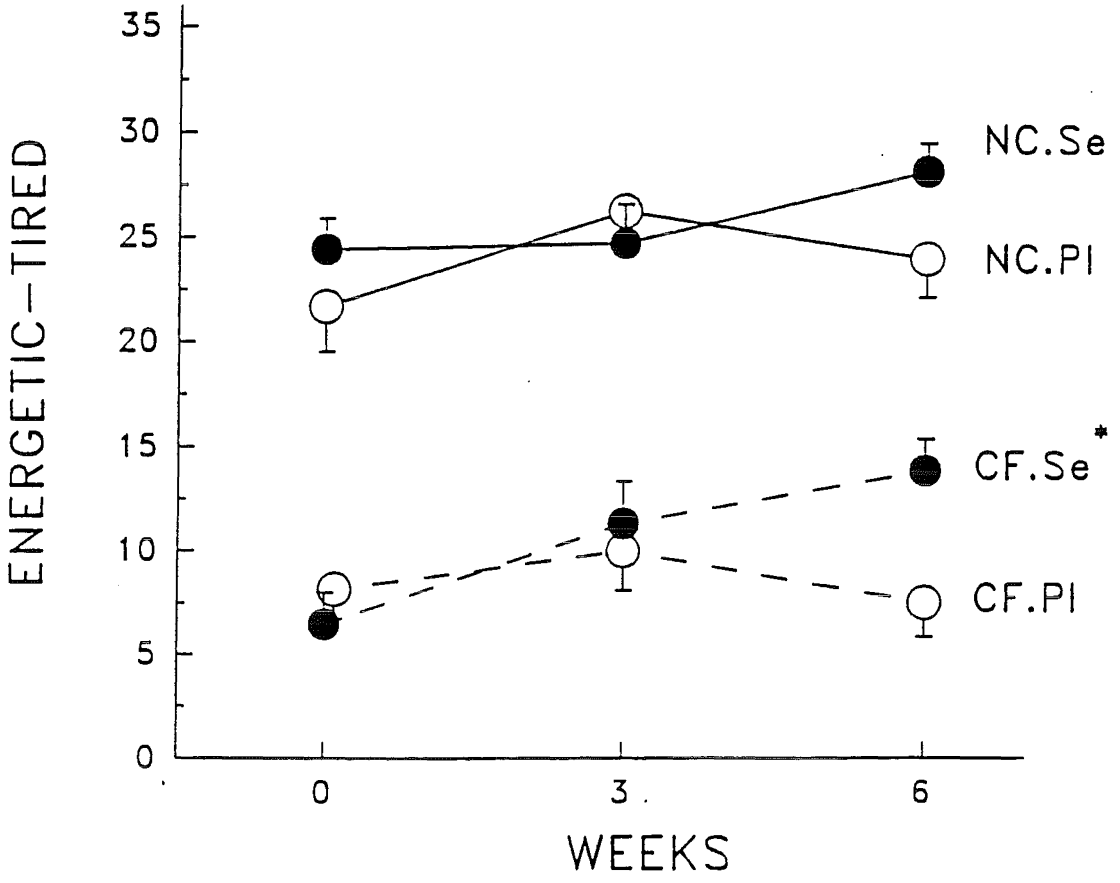
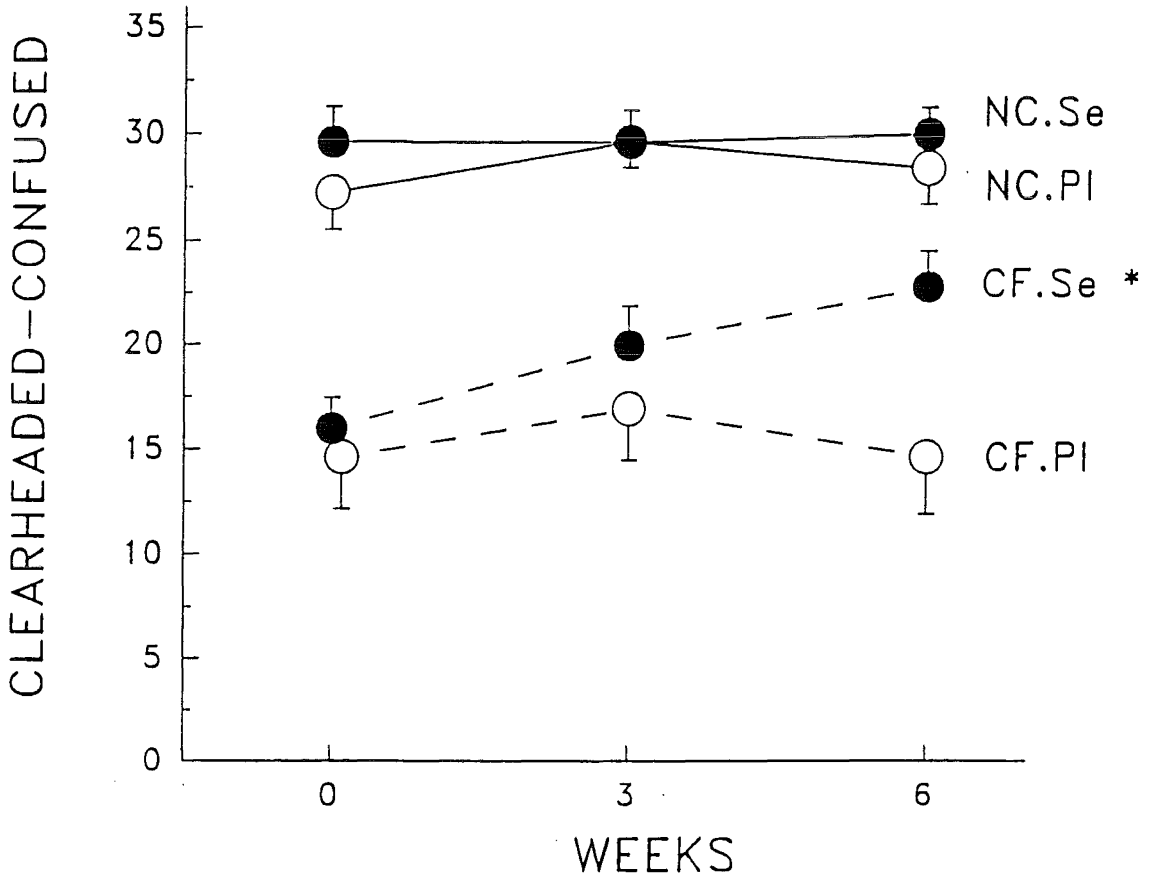


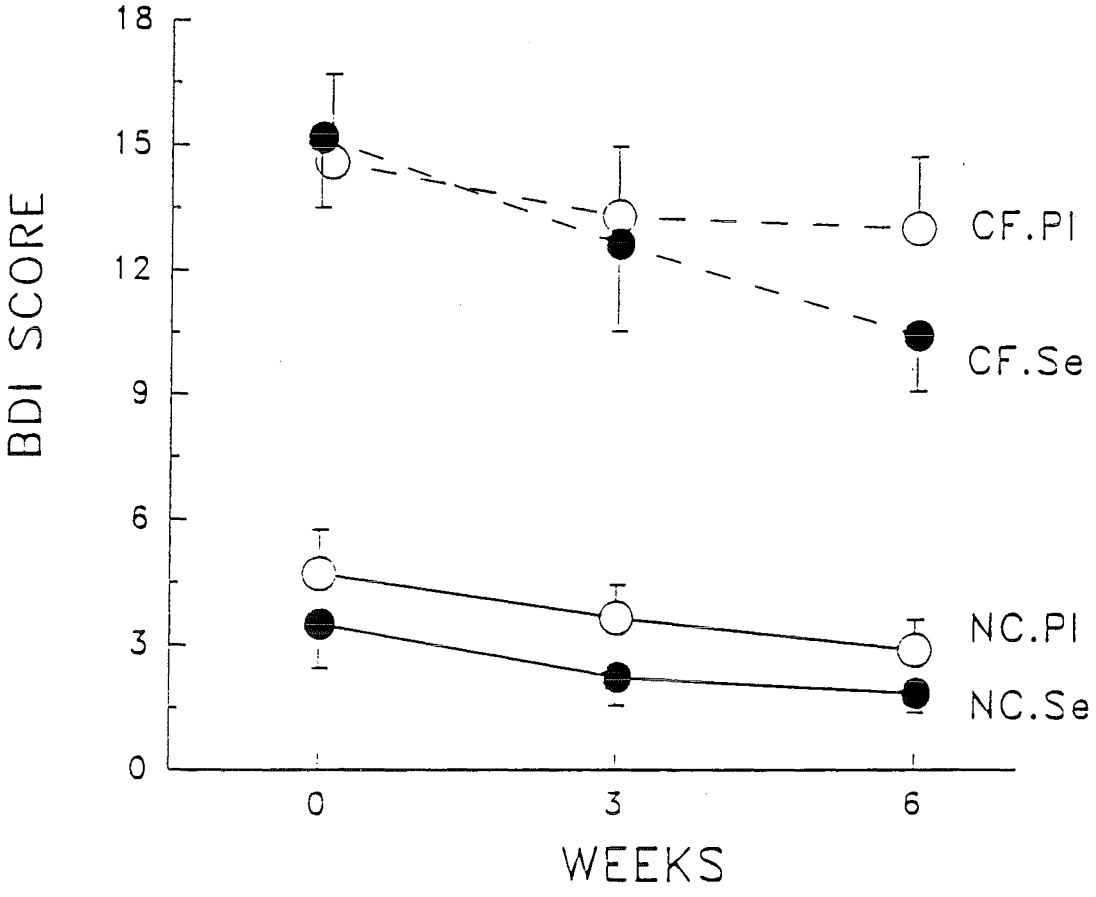
Fig. 15 The Clear Headed - Confused Subscores for CFS and Control



3.10 B.D.I.

These data are shown in Fig. 16. CFS subjects scored considerably higher than controls on the BDI. Analysis of the BDI scores revealed a significant main effect for Group ($F=72.55$;$df=1,64$; $P<0.0001$). Although there was a slight indication that CFS subjects on selenium had reduced scores by week 6 compared to CFS subjects on placebo, the only other significant effect was a Time main effect ($F=8.07$; $df=2,128$;$P<0.001$) due to scores improving for subjects as a whole over weeks.

Fig. 16 Mean BDI Scores for CFS and Control



Chapter 4 DISCUSSION

4.1 DIFFERENCES BETWEEN CONTROL AND CFS SUBJECTS

Consistent with previous findings reported by Hickie et al (1990), Manu et al(1989), Kruesi et al (1989) and Taerk (1987) that CFS subjects are more likely to show depressive symptoms, CFS subjects in the present study also reported higher levels of depressive symptoms as measured by the Beck Depressions Inventory. Indeed Abbey and Garfinkel (1991) suggest that CFS subjects may represent a subgroup of depressive patients.

General mood states, however, have not been reported for this group before. The mean total mood scores for the CFS group was found to be low (90) and according to the manual (Lorr and McNair 1982) was much lower than the average of 144 obtained from an unselected group of presumably healthy subjects. The healthy control subjects in the present study had a mean score of 156 at the start of the study. In addition there was a difference in the profile of mood states between CFS and Control subjects. The component levels for CFS subjects are all relatively low compared to those for controls, but subjects are particularly likely to report more tired than energetic

and more unsure than confident.

4.2 EFFECTS OF SELENIUM IN CONTROLS

Benton and Cook (1990) reported that healthy subjects on selenium supplementation showed a clear and significant improvement in their total mood scores. In the present study however, there was no significant change in total mood score in controls on selenium and there is only a weak suggestion of mood improvement from the analysis of subscores for the composed-anxious and energetic-tired measures. Benton and Cook (1991) also reported that subjects on low diet selenium are likely to show an improvement in mood score following selenium supplementation. However, controls in the present study showed low selenium status as evidenced by the blood measures. Perhaps subjects in Benton and Cooks study had other mineral/vitamin deficits that had to be compensated for by selenium unlike those subjects in the present study.

4.3 EFFECT OF SELENIUM IN CFS SUBJECTS

There was a very marked mood response by CFS subjects in this investigation of selenium supplementation . The change in mood improvement for CFS subjects given selenium was similar to the response found by Benton and Cook with

healthy subjects in Wales. However, although the level of improvement made by CFS subjects in the present study did not attain the level achieved by Benton and Cook's (1990; 1991) healthy subjects when taking selenium, they reached a level comparable to the mood scores shown by the healthy controls that were tested in this study.

However, it also has to remembered that the mood profile of CFS subjects is different from normal subjects and may have led to some differences in response to supplementation. The only reasonable indication that mood improved in controls in the present study was on the energetic-tired score, where as CFS subjects showed improvement on all except the agreeable -hostile score.

Both controls and CFS subjects in the present study showed the characteristically low blood selenium level found in most New Zealand inhabitants and further more the blood level in both groups prior to treatment was the same. Therefore it seems unlikely that low levels are in any simple way was responsible for the CFS syndrome. Perhaps the use of selenium only alleviates the symptom complained of rather than provides a cure. However, it was noticeable that blood selenium levels in CFS subjects increased much more than was seen in controls on selenium. This raises the possibility that a greater amount of selenium is needed by CFS subjects to perhaps reduce their

symptoms or that the controls used here did not obtain high enough levels of selenium to elevate their mood scores. In the absence of any blood results, one can only speculate that Benton and Cooks subjects had higher blood selenium levels than those expected in New Zealand subjects (the average New Zealander has lower blood selenium than the average British subject) and that their blood levels rose considerably after taking selenium.

There may also be other important mineral factors as evidenced by the response of a British group to magnesium supplementation (Cox et al, 1991).

When the present findings are compared to results from other studies that used selenium supplementation, other interesting differences appear. The investigation by Robinson et al (1981) did not find any evidence of improvement in symptoms of muscular pain and tiredness following selenium supplementation in CFS subjects. But, in the present study, the monitoring of CFS mood revealed a significant improvement in the well-being of CFS subjects that were treated with selenium. This difference in response may suggest a somewhat subtle mineral effect with respect to subjects who experience lowered mood states as a result of a decline in other areas of health.

4.4 THE PRESENT STUDY AND ITS LIMITATIONS

The present study has shown evidence that selenium can be

beneficial to the well-being of CFS subjects in terms of raising mood levels. With regard to selenium supplementation, this investigation is in part a replication of Bentons results, but only with respect to the CFS group. However, this type of study, involving selenium and CFS has not been undertaken elsewhere and it may be prudent to await confirmation before placing too much emphasis on the results so far discussed.

But there is also a need to investigate other minerals and vitamins, the effect of varying these as well as the precise effect these minerals might have on the well-being of CFS and healthy subjects.

It would also be important to consider different areas of wellbeing e.g memory and motor deficits found in both CFS (recorded by Smith, 1992) and perhaps healthy/ageing subjects discussed by Benton and Cook (1991). This type of investigation can be useful in identifying some of the basic problems displayed by some of the symptoms of CFS and perhaps healthy subjects.

REFERENCES

Abbey, S E & Garfinkel, P E (1991) Chronic Fatigue Syndrome and the Psychiatrist. Canadian Journal of Psychiatry, 35, 625-633.

Behan, P O, Behan, W M H, & Bell, E J (1985) The Postviral Fatigue Syndrome - an analysis of the findings in 50 cases. Journal of Infection, 10, 211-222.

Bell, E J, McCartney, R A, & Riding, M H (1988) Coxsackie B viruses and myalgic encephalomyelitis. Journal of the Royal Society of Medicine, 81, June, 329-331.

Benton, D & Cook, R (1990) Selenium Supplementation Improves Mood in a Double-blind Crossover Trial. Psychopharmacology, 102, 549-550.

Benton, D & Cook, R (1991) The Impact of Selenium Supplementation on Mood. Biological Psychiatry, 29, 1-7.

Berry, M J, Banu, L & Larsen, P R, (1991) Type I Iodothyronine Deiodinase is a Selenocysteine-Containing Enzyme. Nature, 349, 438-440.

Burk, R F (1989) Recent Developments in Trace Element Metabolism and Function: Newer Roles for Selenium in Nutrition. Journal of Nutrition, 119, 1051-4.

Coombs, G F & Combs, S B (1986). The Role of Selenium in Nutrition. Academic Press, Florida, 1986.

Cox, I M, Campbell, M J & Dowson, D (1991) Red Blood Cell Magnesium and Chronic Fatigue Syndrome. Lancet, 337, 757-760.

Fark, A R (1991) Epstein-Barr Viral Infection. Journal of Family Practice, 32(2), 202, 205-6.

George, P & Walmsley, T (1991) Unpublished Research Proposal. Personal Communication.

Hickie, I, Lloyd, A, Wakefield, D, Parker G (1990) The Psychiatric Status of Patients with the Chronic Fatigue Syndrome. British Journal of Psychiatry, 156, 534-540.

Holmes, M J (1991) Studies of Chronic Fatigue Syndrome in New Zealand - Proposal. University of Otago. Information Sheet. Unpublished article.

Holmes, M J, Chapman, C J, Young, A J, Cross, J P & Niven, B E (1988) Paired Age, Sex and Ethnically Matched Studies of Peripheral Blood Leucocyte Profiles in Early Chronic Fatigue Syndrome. Unpublished paper, University of Otago, Dunedin.

Horne, S (1991) Unpublished Thesis. "Merely Triumphant".

Houston, J C, Joiner, C L & Trounce, J R (1968) A Short Textbook of Medicine, 3d ed, UniBooks, London.

Kroenke, K (1991) Chronic Fatigue Syndrome: Is it Real? Postgraduate Medicine 89(2), 82-46.

Kroenke, K, Wood, D R & Mangelsdorff, A D (1988). Chronic Fatigue in Primary Care: Prevalance, Patient Characteristics, and Outcome. Journal of American Medical Association, 260, 929-934.

Kruesi, M J, Dale, J & Strauss, S E (1989) Psychiatric Diagnosis in Patients who have Chronic fatigue Syndrome. Journal of Clinical Psychiatry 50(4), 148.

Lloyd, A R, Hales, J P & Gandevia, S C (1988) Muscle Strength, Endurance and Recovery in the Post-infection Fatigue Syndrome. Journal of Neurology, Neurosurgery, and Psychiatry, 51, 1316-1322.

Lloyd, A R, Wakefield, D, Boughton C R, et al. (1989). Immunological Abnormalities in the Chronic Fatigue Syndrome. Medical Journal of Australia, 151, 122-124.

Lloyd, A R, Hickie, I, Boughton, C R, Spencer, O & Wakefield, D (1990) Prevalence of Chronic Fatigue Syndrome in an Australian Population. Medical Journal of Australia, 153(9), 522-28.

Logan, J W (1987) Postneonatal Mortality in Christchurch (Letter). New Zealand Medical Journal, 100, 329.

Logan, J W (1988) Trace Elements Iron, Copper and Selenium in Cot Death. Trace Elements in New Zealand: Environmental, Human and Animal. Proc. N.Z. Trace Elements Group Conference Dec. 1988. Lincoln College, Canterbury.

Lorr, M & McNair, D (1982) Profile of Mood States - Manual, Educational & Industrial Testing Service, San Diego.

Lynch, S, Seth, R (1989) Postviral Fatigue Syndrome and the VP-1 Antigen. Lancet, ii, 1160-1161.

MacIntyre, A (1989) M.E. Post-viral Fatigue Syndrome - How to Live with it. Unwin Paperbacks, London.

McEvedy, C P & Beard, A W.(1973) A Controlled Follow-up of Cases Involved in an Epidemic of "Benign Myalgic Encephalomyelitis" British Journal of Psychiatry, 122, 141-150.

McEvedy, C P & Beard, A W (1970) Royal Free Epidemic of 1955: a reconsideration. British Medical Journal, 1, 7-11.

McEvedy, C P & Beard A W (1970) Concept of Benign Myalgic encephalomyelitis. British Medical Journal, 1, 11-15.

McNair, D M, Lorr, M & Droppleman, L F (1981) Eits for the Profile of Mood States. Educational & Industrial Testing Service, California, 1981.

Manu, P, Matthews, D A, Lane, T J, Tennen, H, Hesselbrock, V, Mendola, R & Affleck, G (1989) Depression Among Patients with Chief Complaint of Chronic Fatigue. Journal of Affective Disorders, 17 165-172

Merck Manual, (1987), Ed. by Berkow, R, & Fletcher, A J 15th Ed.1987, Merck Sharp & Dohme Research Laboratories, New Jersey.

Money, D F L (1970) Vitamin E and Selenium Deficiencies and their Possible Etiological Role in Sudden Infant Death Syndrome. New Zealand Medical Journal, 71, 32-34.

Mukherjee, T, Smith, K, & Maros, K, (1987) Abnormal Red Blood Cell Morphology in Myalgic Encephalomyelitis. Lancet, ii, 328-32.

Murdoch, J C (1992) Feature Article. Otago Daily Times, 6 May, 1992.

Murdoch, J C (1987) Myalgic Encephalomyelitis (ME) Syndrome - An analysis of the Clinical Findings in 200 Cases. N Z Family Physician, 14, 51-54.

Passwater, R A (1980) Selenium as Food and Medicine. Keats Publishing, Connecticut, 1980.

Prasher, D (1990) Sensory and Cognitive Event-Related Potentials in Myalgic Encephalomyelitis. Journal of Neurology, Neurosurgery, and Psychiatry, 53, 247-253.

Ramsay, A M (1957) Encephalomyelitis Simulating Poliomyelitis and Hysteria. Lancet ii, 1196-1200.

Ramsay, A M (1978) Epidemic Neuromyasthenia. Postgraduate Medical Journal, 54, 718-21.

Ramsay, A M (1986) Postviral Fatigue Syndrome - the saga of Royal Free Disease. London, Gower Medical Publishing, 1986.

Robinson, M F (1988) 1988 McCollum Award Lecture. The New Zealand Selenium Experience. American Journal of Clinical Nutrition, 48, 521-534.

Robinson, M F, Campbell, D R, Stewart, RDH, Rea, H M, Thomson, C D, Snow, P G & Squires, IHW (1981) Effect of Daily Supplements of Selenium on Patients with Muscular Complains in Otago and Canterbury. New Zealand Medical Journal, 93(683) 289-292.

Robinson, J R, Robinson, M F, Levander, O A, Thomson, C D (1985) Urinary Excretion of Selenium by New Zealand and North American Human Subjects on Different Intakes. American Journal of Clinical Nutrition, 41, 1023-31.

Robinson, M F, Thomson, C D & Huemmer, P K (1985) Effect of a Megadose of Ascorbic, a Meal and Orange Juice on the Absorption of Selenium as Sodium Selenite. New Zealand Medical Journal 98(784) 627-629.

Rosenzweig, M R & Leiman, A L (1989) Physiological Psychology, 2d ed, Random House, New York, 1989.

Shepherd, C (1989) Living with M.E. - A self-help guide. Cedar, London, 1989.

Simpson, L (1990) Are M.E. and C.F.S. the Same Disease? New Zealand Medical Journal, 103, 305.

Simpson, L (1991) The Role of Non-discocytic Erythrocytes in the Pathogenesis of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome. Unpublished article, personal communication.

Smith, A P (1992) Chronic Fatigue Syndrome and Performance, Chapter 10, In Hand book of Human Performance Volume II.

Snow, P, Poore, M & Paul, P (1984) An unexplained illness in West Otago. New Zealand Medical Journal, 97, 351-354.

Snow, P (1984) West Otago Illness. New Zealand Medical Journal, 33, 502.

Spallholz, J E (1989) Nutrition: Chemistry and Biology, Prentice Hall, New Jersey, 1989.

Taerk, G S, Toner, B B,Salit, I E, et al (1987) Depression in Patients with Neuromyasthenia. International Journal Psychiatry Medicine, 17, 49-56.

Thomson, C D (1991) Clinical Consequences and Assessment of Low Selenium Status. Leading Article, New Zealand Medical Journal, September 376-377.

Thomson, C D & Robinson, M F (1980) Selenium in Human Health and Disease with Emphasis on those Aspects Peculiar to New Zealand. American Journal of Clinical Nutrition, 33, 303-323.

Thomson, C D & Robinson, M F (1986) Urinary and Faecal Excretions and Absorption of a Large Supplement of Selenium: Superiority of Selenate over Selenite 1-3. American Journal of Clinical Nutrition, 44, 659-63.

Thomson, C D & Robinson, M F (1988) Food Concentrations and Dietary Intakes of Selenium in Otago, New Zealand. Trace Elements in New Zealand: Environmental, Human and Animal. Proc. N.Z. Trace Elements Group Conf. 30 Nov.-2 Dec, Lincoln Coll. Canterbury.

Trotter, B (1978) The Rape of our Heritage. Timaru Herald Company Ltd. Timaru 1978.

Watkinson J H (1974) The Selenium Status of New Zealanders. New Zealand Medical Journal, 80, 202-205.

Watkinson J H (1962) Soil Selenium and Animal Health. Trans int Soc Soil Sci, Comm. iv & v 149-154.

Winterbourne, C C, Saville, D J & George, P M (1992) Increase in Selenium Status of Christchurch Adults Associated with Deregulation of the Wheat Market. In press.

APPENDIX

TABLE:

CFS SUBJECTS / DURATION AND HISTORY OF ILLNESS
Reported factors that may have precipitated Chronic Fatigue Syndrome

CODE	AGE	yr	1st sign	History
1E	37	1.5		kidney stones, headaches, sensitive to noise & temp.
2E	36	3	migraines	kidney stones, sleepless
3E	43	6.5	flu	muscls fat. mental stress
4E	26	4	flu	fatigue, allergies,sleepless
5E	42	11	stress	migraines, allergies
6E	43	8	toxic sprays	glan.fever, bowel irrit.
7E	45	8		nausea,fatigue,caesar
8E	46	4	headaches	fatigue, headaches
9E	18	10	from parents	asthma, allergies
10E	43	3		fatigue, headaches
11E	44	8		allergies, fatigue
13E	29	3	flu '79	tonsils aged 4
14E	43	7	fatigue,	depress. headach. sleepl
15E	44	3	blood tran.	Hysterect '84
16E	38	2.5	glan.fever	kidney stones, arthritis, hepatits, pneum.appendic.
19E	49	2	famil trauma	sleeplessness
21E	58	6	virus sprays	arthritis bronch.mumps,etc
22E	36	14	virus	chicken pox meas.mumps allergic penicilin, oranges. sleeplessness
23E	52			fatigue, mem.loss, irr.bowel depression, visual disturb.
24E	43	9	virus	sinus allergies
25E	19	4.5	gland. fever	bow.irr
26E	42	2.5	mental fatig	sleepl. memory loss
28E	29	8	muscl.disor.	gallbladder,glan.fever
29E	41	1		asthma, tonsils,PMS allerg.
30E	30	3		Leptospirosis, ashthma
32E	20	o.5	bronchitis	disturbed sleep.
33E	32	3		allergies, sleeplessness

TABLE: (cont.)
CFS SUBJECTS / HISTORY OF ILLNESS

CODE	AGE	yr	1st sign	History
35E	33	5	glan.fever	Hp virus fatigue, sleepl.
39E	50	8	lead poisoning	Eng.measles, flu, chicken pox mumps sleeplessness
40E	54	3.5	stress, g. fever	scarlet fever, mumps, chicken pox .pneumonia, depression
41E	46	5	car acci. stress	sleeplessness allergies
46E	22	5	glan.fever	sleepless, allerg. mem.loss
48E	23	6	virus	appendicitis, stomach probl.
49E	35	6		tonsil, allerg. mood changes
50E	40	6		gland.f.ovarian cysts

Department of Psychology
University of Canterbury Christchurch New Zealand
Telephone: (03) 667-001
Fax: (03) 642-181

DEPARTMENT OF PSYCHOLOGY UNIVERSITY OF PSYCHOLOGY

CONSENT FORM

Brief Description of Project:
This project will investigate the possible influence of a mineral supplement on various mood states and levels of fatigue, using simple standard questionnaires, in a group of people who have been diagnosed as suffering from a chronic fatigue syndrome called Myalgic Encephalomyelitis (ME) and in a group of healthy, non-ME subjects.

Risks Associated with Participation:
The mineral used is a naturally occurring one that will be in an otherwise neutral tablet (e.g., no yeast or vitamins). The proposed quantity of daily mineral intake is well within safe recommended limits for maintaining good health according to the American Food and Nutrition Board (1980) and thus should not pose any health risks to ME or non-ME participants.

Time Required:
Each participant is asked to take a single tablet on a daily basis for two six-week periods, with a duration of 5 months intervening between each six-week period. To enable us to be certain that any effects on mood obtained can be attributed to the mineral, participants will be given **either** the mineral tablet **or** a tablet with no mineral content during the first six-week period, followed by administration of the alternate tablet on the second six-week period. Participants will be required to spend half an hour (max one hour) answering the questionnaires at the beginning, midway and end of each six-week period. In addition, for each participant who is willing, a small sample of blood will be obtained by medical personnel at the beginning and end of each six-week period to determine the blood levels of the mineral under study.

Name of Researcher:
Boyd (Hank) Scott

Name of Supervisor:
Dr John Dalrymple-Alford

I agree to participate in the project described above, on the understanding that if at any time I wish to withdraw from the study I may, without prejudice, do so. All personal information collected will be confidential as will the identity of the participants.

Name: _____
(Please Print)

Signature: _____ Date: _____

E _____ DATE _____

IDENTIFICATION

ow are words that describe feelings and moods people have. Please read EVERY word carefully. Then fill NE space under the answer which best describes how you have been feeling DURING THE PAST WEEK LUDING TODAY.

pose the word is *happy*. Mark the one answer which is closest to how you have been feeling DURING PAST WEEK INCLUDING TODAY.

The numbers refer to these phrases:

0 = Much unlike this
1 = Slightly unlike this
2 = Slightly like this
3 = Much like this

MARKING DIRECTIONS

- USE A NO. 2 PENCIL ONLY.
- MAKE NO STRAY MARKS.
- ERASE CLEANLY.

CORRECT MARK ⓪①②● INCORRECT MARK ⊗✓◉◒

MUCH UNLIKE THIS / SLIGHTLY UNLIKE THIS / SLIGHTLY LIKE THIS / MUCH LIKE THIS			
Composed .. ⓪①②③	19. Vigorous..... ⓪①②③	37. Serene..... ⓪①②③	55. Ready-to-go ... ⓪①②③
Angry ..... ⓪①②③	20. Dejected..... ⓪①②③	38. Bad tempered . ⓪①②③	56. Discouraged ... ⓪①②③
Cheerful..... ⓪①②③	21. Kindly..... ⓪①②③	39. Joyful..... ⓪①②③	57. Good-natured . ⓪①②③
Weak ..... ⓪①②③	22. Fatigued..... ⓪①②③	40. Self-doubting .. ⓪①②③	58. Weary ..... ⓪①②③
Tense ..... ⓪①②③	23. Bold..... ⓪①②③	41. Shaky ..... ⓪①②③	59. Confident ..... ⓪①②③
Confused.... ⓪①②③	24. Efficient ..... ⓪①②③	42. Perplexed ..... ⓪①②③	60. Businesslike ... ⓪①②③
Lively ..... ⓪①②③	25. Peaceful..... ⓪①②③	43. Active..... ⓪①②③	61. Relaxed..... ⓪①②③
Sad ..... ⓪①②③	26. Furious ..... ⓪①②③	44. Downhearted .. ⓪①②③	62. Annoyed ..... ⓪①②③
Friendly..... ⓪①②③	27. Lighthearted .. ⓪①②③	45. Agreeable..... ⓪①②③	63. Elated..... ⓪①②③
Tired..... ⓪①②③	28. Unsure..... ⓪①②③	46. Sluggish..... ⓪①②③	64. Inadequate..... ⓪①②③
Strong ..... ⓪①②③	29. Jittery ..... ⓪①②③	47. Forceful..... ⓪①②③	65. Uneasy ..... ⓪①②③
Clearheaded . ⓪①②③	30. Bewildered.... ⓪①②③	48. Able to concentrate ⓪①②③	66. Dazed..... ⓪①②③
Untroubled .. ⓪①②③	31. Energetic..... ⓪①②③	49. Calm..... ⓪①②③	67. Full of pep ..... ⓪①②③
Grouchy ..... ⓪①②③	32. Lonely ..... ⓪①②③	50. Mad ..... ⓪①②③	68. Gloomy..... ⓪①②③
Playful ..... ⓪①②③	33. Sympathetic .. ⓪①②③	51. Jolly ..... ⓪①②③	69. Affectionate.... ⓪①②③
Timid ..... ⓪①②③	34. Exhausted .... ⓪①②③	52. Uncertain ..... ⓪①②③	70. Drowsy ..... ⓪①②③
Nervous ..... ⓪①②③	35. Powerful..... ⓪①②③	53. Anxious..... ⓪①②③	71. Self-assured... ⓪①②③
Mixed-up .... ⓪①②③	36. Attentive ..... ⓪①②③	54. Muddled..... ⓪①②③	72. Mentally alert.. ⓪①②③

BE SURE YOU HAVE ANSWERED EVERY ITEM

SCANTRON FORM NO. T-101269-POMS 4987-0911-5 4 3 2

I don't feel I look any worse than I used to.

I am worried that I am looking old or unattractive.

I feel that there are permanent changes in my appearance that make me look unattractive.

I believe that I look ugly.

I can work about as well as before.

It takes an extra effort to get started at doing something.

I have to push myself very hard to do anything.

I can't do any work at all.

I can sleep as well as usual.

I don't sleep as well as I used to.

I wake up 1-2 hours earlier than usual and find it hard to get back to sleep.

I wake up several hours earlier than I used to and cannot get back to sleep.

I don't get more tired than usual.

I get tired more easily than I used to.

I get tired from doing almost anything.

I am too tired to do anything.

My appetite is no worse than usual.

My appetite is not as good as it used to be.

My appetite is much worse now.

I have no appetite at all anymore.

19

I haven't lost much weight, if any, lately.

I have lost more than 5 pounds.

I have lost more than 10 pounds.

I have lost more than 15 pounds.

I am purposely trying to lose weight by eating less. Yes _____ No _____

20

I am no more worried about my health than usual.

I am worried about physical problems such as aches and pains; or upset stomach; or constipation.

I am very worried about physical problems and it's hard to think of much else.

I am so worried about my physical problems that I cannot think about anything else.

21

I have not noticed any recent change in my interest in sex.

I am less interested in sex than I used to be.

I am much less interested in sex now.

I have lost interest in sex completely.

_____ Subtotal Page 2

_____ Subtotal Page 1

_____ Total Score

BDI

Date: _____

ame: _____ Marital Status: _____ Age: _____ Sex: _____

cupation: _____ Education: _____

is questionnaire consists of 21 groups of statements. After reading each group of statements carefully, cle the number (0, 1, 2 or 3) next to the one statement in each group which **best** describes the way you ve been feeling the **past week, including today.** If several statements within a group seem to apply equally ll, circle each one. **Be sure to read all the statements in each group before making your choice.**

- I do not feel sad.
- I feel sad.
- I am sad all the time and I can't snap out of it.
- I am so sad or unhappy that I can't stand it.

- I am not particularly discouraged about the future.
- I feel discouraged about the future.
- I feel I have nothing to look forward to.
- I feel that the future is hopeless and that things cannot improve.

- I do not feel like a failure.
- I feel I have failed more than the average person.
- As I look back on my life, all I can see is a lot of failures.
- I feel I am a complete failure as a person.

- I get as much satisfaction out of things as I used to.
- I don't enjoy things the way I used to.
- I don't get real satisfaction out of anything anymore.
- I am dissatisfied or bored with everything.

- I don't feel particularly guilty.
- I feel guilty a good part of the time.
- I feel quite guilty most of the time.
- I feel guilty all of the time.

- I don't feel I am being punished.
- I feel I may be punished.
- I expect to be punished.
- I feel I am being punished.

- I don't feel disappointed in myself.
- I am disappointed in myself.
- I am disgusted with myself.
- I hate myself.

8
- I don't feel I am any worse than anybody else.
- I am critical of myself for my weaknesses or mistakes.
- I blame myself all the time for my faults.
- I blame myself for everything bad that happens.

9
- I don't have any thoughts of killing myself.
- I have thoughts of killing myself, but I would not carry them out.
- I would like to kill myself.
- I would kill myself if I had the chance.

10
- I don't cry any more than usual.
- I cry more now than I used to.
- I cry all the time now.
- I used to be able to cry, but now I can't cry even though I want to.

11
- I am no more irritated now than I ever am.
- I get annoyed or irritated more easily than I used to.
- I feel irritated all the time now.
- I don't get irritated at all by the things that used to irritate me.

12
- I have not lost interest in other people.
- I am less interested in other people than I used to be.
- I have lost most of my interest in other people.
- I have lost all of my interest in other people.

13
- I make decisions about as well as I ever could.
- I put off making decisions more than I used to.
- I have greater difficulty in making decisions than before.
- I can't make decisions at all anymore.

_____ Subtotal Page 1

CONTINUED ON BACK

THE PSYCHOLOGICAL CORPORATION
HARCOURT BRACE JOVANOVICH, INC.

9-018359

INFORMATION SHEET

You are being asked to take part as a volunteer in the following research

This study is being conducted so that an understanding of the stress, feeling of tiredness and fatigue and associated moods of depression and anxiety can be evaluated in relation to a specific mineral supplementation in the daily diet of Myalgic Encephalomyelitis subjects

It is also carried out as part fulfilment of a Thesis requirement for the Master of Science degree in Psychology at the University of Canterbury.

WHAT WILL YOU BE EXPECTED TO DO

Your stress and mood states will be evaluated both before, during and after each six week trial period. This evaluation will require your filling out a couple of questionnaires.

Blood samples will also be collected from willing subjects so that a check on mineral blood levels can be performed.

The mineral supplementation period will involve your taking of a single pill each day for six weeks. After the first six weeks trial you will be ona five month wash-out period when you will be free from any mineral pills.

The whole procedure is then repeated for another six weeks.

HOW MUCH TIME WILL IT TAKE?

About eight months in total from start to finish.

WHAT ARE THE RISKS

There are no anticipated risks to subjects in this study.

WILL THE INFORMATION BE CONFIDENTIAL?

The identity of each subject and any information they supply for the study will remain confidential at all times.

CAN YOU WITHDRAW AT ANY TIME?

Each subject is free to withdraw anytime from any part or all of the research programme without prejudice to any present or future treatment.

WHO SHOULD YOU DISCUSS THIS WITH?

You should feel free to discuss this programme with other members of your ME support group and a close relative or friend. You should also contact your own physician should you feel the need for medical consultation. In this respect I will be available to discuss the programme with other support services you make contact with.

Dr John Dalrymple-Alford (Department Psychology, University of Canterbury) will also be available for consultations in respect to this study.

DEBRIEFING PROCEDURE

Each subject will be notified of the results of this study. They will be told of the actual mineral they took and when they were on it during the study. Any relevant results of blood tests will also be made known where applicable. The overall result of the programme will be explained to all subjects when the results have been fully analysed.

DEPARTMENT OF PSYCHOLOGY, UNIVERSITY OF CANTERBURY

CONFIDENTIAL SUBJECT QUESTIONNAIRE(EX)

NAME: _____ _____MR/MRS/MISS
(Surname) (First Name)
DATE OF BIRTH_____PHONE_____

TOWN & COUNTRY OF BIRTH: _____ _____

RACE OR ETHNIC ORIGIN: _____AGE: ____

****

1. How long is it since you were first diagnosed as having ME/CFS? _____
2. Name of doctor who made the diagnosis? _____
3. Where have you lived most of your life? _____
4. In the last five years? _____
5. Brief summary of past illnesses not related to ME _____

   _____

   _____
6. Present level of ME condition (High/Medium/Low/Non-existent)?_____
7. How often do these bouts recur? _____
8. Any major operations? _____
9. Number of pregnancies? ___ Number of children? ___ Age of eldest? ___
10. Does any other relative have ME or have had it? YES/NO (Give relationship, e.g. sister, uncle, etc) _____
11. Level of Active Participation in cultural and Sporting Interests:

    (a) List sports involved in at present: _____

    _____

    (b) List past involvement in sports: _____

    (c) List cultural activities engaged in at present, e.g. tramping, Bridge, etc.

    _____

    (d) List past cultural activities no longer involved in: _____

(PLEASE TURN OVER THE PAGE)

12. Sleep Patterns:

Give any changes in sleep habits since contacting ME: _____

_____

13. Is there any part of the day you feel more active? _____

_____

14. Do you feel better any particular months of the year? _____

_____

15. Eating Habits: (Please be "precise" in your answers to this question)

(a) List dislikes: _____

(b) List major source of the following - indicate how often they are consumed (per week, month, etc.)

(i) Proteins: (cheese, fish, eggs, meat (type))

_____

_____

_____

(ii) Carbohydrates: (sugars, starches) _____

_____

_____

(iii) Fluids: _____

_____

(iv) Fruits & Cereals: _____

_____

(NEXT PAGE PLEASE)

THE FOLLOWING IS AN OPTIONAL SECTION WHICH WOULD BE HELPFUL TO OUR STUDY DESIGN:

A. Years of secondary schooling completed: _____

B. Years of tertiary (technical/university) schooling completed: _____

C. What is your present occupation? _____

D. What other occupations have you held? _____

_____

E. Have you ever lost a job because of ME/CFS? _____ Explain: _____

_____

F. What in your view may have started your ME/CFS condition? _____

_____

_____

G. Are your family and close friends sympathetic and supportive of your situation since your ME/CFS diagnosis?

_____

H. HEIGHT_____ WEIGHT_____

Date: _____

Thank you for completing this questionnaire and your support in this work.

B ,H SCOTT

Please return to: 13 Kingslea St. Oamaru

(c) List any mineral and vitamin supplement (Please give brand name(s) and no. of taken daily):

(i) Currently Using: _____

_____

_____

(ii) Were Using: _____

_____

_____

(iii) Special Diets: (Indicate any professional advice) _____

_____

_____

16. Allergies: _____

_____

_____

17. Any Other Significant Changes to Your Health Since Contacting ME? _____

_____

_____

18. Name of Present Doctor: _____

Address/Surgery: _____

Phone: _____

YOUR ADDRESS _____

_____

(PLEASE TURN OVER THE PAGE)