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THE INTEGRITY OF THE CIRCADIAN TIME-KEEPING SYSTEM IN
CHRONIC FATIGUE SYNDROME

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B.B.Sc. (Hons) (La Trobe University)
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Submitted in fulfilment of the requirements for the degree
of
Doctor of Philosophy
Deakin University
August 2000
DEAKIN UNIVERSITY
CANDIDATE DECLARATION

I certify that the thesis entitled:

'The integrity of the circadian time-keeping system in chronic fatigue syndrome'

Submitted for the degree of:

Doctor of Philosophy

Is the result of my own research, except where otherwise acknowledged, and that this thesis in whole or in part has not been submitted for an award, including a higher degree, to any other university or institution.

Full Name Gregory Allan Tooley

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Acknowledgments

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Abstract

Chronic Fatigue Syndrome (CFS) is a debilitating condition in which severe, ongoing fatigue is the most prominent of a complex of somatic, psychological and neuropsychological symptoms. The aetiology of CFS remains uncertain and, to date, efforts to distinguish a clear pathophysiological profile for the disorder have been unsuccessful. Current evidence suggests that, rather than being a discrete disease entity with a single cause, CFS is a clinical condition resulting from the interaction of a number of pathophysiological factors, including acute infections, stress and psychiatric disorder. Recently, there has been some interest in the proposition that disordered circadian time-keeping may contribute to the development and/or course of the illness. The rationale for the investigation of circadian factors in CFS is based on the fact that disorders known to be associated with circadian dysregulation, such as jet lag and shift-work related syndromes have a high degree of symptomatological overlap with CFS. Also, the presence of circadian disturbance could account, in part, for other phenomenological aspects of CFS, including the high rates of comorbid affective disturbance, and the reports of low-level immune dysregulation among sufferers. While several recent studies have produced some evidence of chronobiological dysregulation in CFS patients, much work remains before conclusions can be drawn about the presence, nature and clinical significance of circadian disturbance in CFS. This thesis describes a series of studies that were designed to systematically investigate: 1. whether CFS is associated with a state of circadian dysregulation, and 2. whether circadian dysregulation contributes significantly to the symptomatology of CFS. The first of the 5 studies reported here compared the circadian patterns of sleep-activity of CFS sufferers with those of healthy controls. Results indicated that CFS patients’ sleep-activity cycles were significantly phase delayed compared to controls, and that some aspects of their circadian profiles of sleep-activity were related to some measures of sleep-disturbance and well-being. Studies 2 and 3 investigated the relationship between rhythms of sleep-wake and core temperature in CFS patients and healthy controls. The major finding from these studies was that sleep-wake and core temperature rhythms appear to be less effectively synchronised. Further evidence was collected that suggested that there was a relationship between circadian parameters and symptom measures in the CFS group.
While this indicated that circadian dysregulation is linked in some way to the symptoms of CFS, assessment of the actual clinical significance of circadian disturbances required the use of a prospective methodology. The final two studies, therefore, report on a placebo-controlled trial of clinical interventions that were designed to restore circadian integrity to CFS patients, in order to see whether this would lead to a reduction in symptom number or severity. Results indicated that, although patients experienced improvements across a range of measures of symptoms and functional capacity, these were small in magnitude, of unlikely clinical significance, and no greater, in general, to improvements reported by patients who underwent placebo treatment. These results, along with those of the earlier studies, are discussed with respect to their implications regarding the presence and significance of circadian dysregulation. It is concluded that, while they provide evidence that CFS is associated with a degree of both internal and external circadian desynchrony, these findings suggest that circadian dysregulation is likely to be only a peripheral, contributor to the processes that generate and maintain the symptom complex. These findings are discussed with respect to how they contribute to our overall understanding of this multi-dimensional condition, and the implications they have for the continuing effort to investigate the causes and treatment of CFS.
OVERVIEW OF THESIS CONTENT
AND STRUCTURE
The primary aim of this thesis is to report on the results of a series of studies that investigated the integrity of circadian organisation in people who suffer from chronic fatigue syndrome (CFS). As will be discussed in the first chapter, CFS is an enigmatic diagnosis that has been the subject of substantial controversy in professional and public circles for a considerable time. In fact, the controversy existed well before the United States' Centers for Disease Control published their first definition of the condition, just over a decade ago (Holmes et al., 1988).

Chapter 1 provides a historical perspective on CFS, with respect to both the scientific and social factors that have, over the last century or so, influenced the way that the condition has been conceptualised and defined. Discussion will focus on the fact that much of the scientific and social phenomena associated with CFS over the past two decades represents, in many respects, a repetition of history. A number of analogous syndromes that have been recorded over the past two and a half centuries, all with persistent, unexplained fatigue as their central feature, will be reviewed. It will be argued that, in order to progress our understanding of CFS, it is necessary to develop an appreciation of the factors that led to the repeated rise and demise of these antecedent syndromes.

Chapter 2 describes our current understanding of the epidemiology of CFS, and of its social and economic impact on individuals and the community in general. It will be outlined that, regardless of the controversy pertaining to the nature of the factors that cause and maintain CFS, it is clear that a substantial number of people suffer
considerable discomfort, disability, and reduced quality of life as a result of the condition.

Chapter 3 reviews the empirical literature with respect to what is currently understood about the factors that contribute to the development and persistence of CFS. It will be concluded that, while many questions about these issues remain, it has become clear that the condition is the endpoint of a complex interaction of a number of predisposing, precipitating and perpetuating factors, arising variously from physiological, psychological and social domains. As a result, attempts to understand and/or treat the CFS require a multidimensional, biosocial approach.

Chapter 4 then builds a rationale for the investigation of circadian dysregulation as one of the factors that may contribute to the complex process that underlies the generation and maintenance of CFS. An outline of the purpose and function of the circadian system is provided, followed by a brief review of disorders associated with the loss of circadian integrity at one level or another. Parallels between the symptoms associated with circadian dysregulation and those that characterise CFS are drawn, and the potential explanatory power of the hypothesis that CFS is associated with circadian disturbance is discussed. On this basis, it is argued that further investigation of the integrity of the circadian systems of CFS sufferers is warranted. A proposal is then put forward to systematically assess the integrity of the circadian timing system in people who suffer from CFS.
Chapter 5 describes the first study of the thesis, in which evidence is obtained that indicates that the sleep-activity cycles of people diagnosed with CFS systematically differ from those of healthy individuals. Results are presented that also suggest that these abnormalities are significantly related to some of the symptoms of the disorder. Chapter 6 then reports on an investigation of the level of coordination between environmental, behavioural and physiological cycles in CFS patients compared to healthy controls. Although some support is found for the hypothesis that CFS is associated with a degree of internal circadian desynchrony, conclusions are limited by relatively low participant numbers and a lack of environmental controls.

A larger, laboratory study was therefore conducted in order to obtain more conclusive information about the relationship between sleep-wake and physiological rhythms in CFS patients. Chapter 7 describes the results of this investigation, which repeat the findings presented in Chapter 6 and offer further evidence of a relationship between circadian dysregulation and the symptoms of CFS.

While it will be suggested that the results of the first three studies indicate that some of the symptoms of CFS are linked with altered circadian function, it will be noted that this evidence alone is insufficient to develop an understanding of the clinical significance of circadian dysregulation in CFS patients. Chapter 8 describes an attempt to prospectively address the question of whether circadian dysregulation is a significant factor in CFS. It is assumed that, if circadian dysregulation is causally linked to the production and/or maintenance of the symptoms of CFS, then treatments designed to promote circadian integrity will result in a reduction in the
intensity and/or number of symptoms. Although the circadian interventions described in Chapter 8 were associated with improvements in aspects of symptomatology and function, these were small in magnitude, of unlikely clinical significance, and mostly matched by a group receiving placebo treatment. A six-month follow-up (Chapter 9) suggested that circadian interventions had no long-term impact on the health or functional capacity of CFS patients. Reasons for the lack of treatment effects are discussed.

Chapter 10 provides an overall discussion of the five studies, and interprets the findings with respect to the evidence regarding the presence and clinical significance of circadian dysregulation in CFS. An attempt is made to develop a theoretical model of the aetiology and impact of circadian dysregulation in CFS. Finally, results are discussed within the overall context of CFS as a complex and multifaceted process, and avenues for future research are outlined.
CHAPTER 1

HISTORICAL PERSPECTIVE
Chronic fatigue syndrome (CFS) is an enigmatic diagnosis that has been the subject of considerable controversy in the scientific and broader communities over the past two decades. While the issues that fuel debate and confusion about the condition are complex, the fundamental problem is that the symptoms that sufferers commonly report appear to be out of all proportion to objective indices of their physical health. This paradox, otherwise stated as the presence of a particular set of symptoms in the absence of medical explanation, defines the illness to such an extent that it forms the basis of the current internationally agreed upon diagnostic criteria (Fukuda et al., 1994).

One of the consequences of the persistent absence of definitive explanations of the illness has been, in the view of some researchers and professionals, its invalidation as a diagnostic entity. Another has been the enormous array of theories and evidence put forward by clinicians and researchers of diverse backgrounds. Inevitably, the collected body of research and opinion on CFS contains many inconsistencies, paradoxes, dead ends and other traps that make it very difficult to navigate effectively. Perhaps more than is the case for most other fields, an appreciation of the scientific and social history of the area is vital in order to provide the researcher or clinician with a context from within which to evaluate the multitude of claims and counter-claims regarding the nature of the disorder, and to assist them to avoid repetition of some of the well-documented mistakes of the past.
The aim of this chapter is to provide a brief historical overview of the events that have been instrumental in the way the field has developed. This commences with an account of the rise, and subsequent fall, in popularity of the late 19th Century diagnosis of 'neurasthenia', and the remarkable parallels that this story has with that of CFS. The discussion will then focus on how, despite its fall from favour in the earlier parts of the 20th Century, the historical threads that link neurasthenia with CFS continued, through a series of different diagnostic labels that were proposed to account for cases of unexplained fatiguing illness, but which could not be sustained empirically. Finally, the rise of CFS as the contemporary label for the same clinical condition as that previously described as neurasthenia will be reviewed, as will the importance of the lessons that can be drawn from the demise of its predecessors.

*The Rise and Fall of Neurasthenia*

Many people see CFS as a disorder of the late 20th Century. This is understandable for several reasons, mainly for the fact that the name itself was first applied just over a decade ago (Holmes et al., 1988) and that the media have only focused on the disorder in the past 15 years. However, for at least the last 250 years, there have been accounts of clinical conditions in which unexplained debilitating fatigue has been accompanied variously by constellations of somatic and psychological symptoms of the type that are associated with CFS as it is defined today. Although historical accounts differ with
respect to some of the details, there is general agreement regarding the individuals and events that have significantly influenced the way that CFS and similar syndromes have come to be regarded by both the scientific and wider communities.

Indeed, much of the phenomenology associated with the rise to prominence of CFS over the past ten to fifteen years is remarkable for the way it has so closely replicated events of over a century ago, following the introduction of ‘neurasthenia’ (nervous exhaustion) to medical terminology in the late 19th Century. George Miller Beard, a neurologist from New York, published the original description of the illness in 1869 (Beard, 1869), in which he provided diagnostic guidelines that bear a significant resemblance to the current consensus criteria for CFS (Fukuda et al., 1994). Diagnosis was achieved ‘partly by the positive symptoms and partly by exclusion’ (p.218). Complaints of ‘general malaise, debility of all the functions, poor appetite, abiding weakness in the back and spine, fugitive neuralgic pains, hysteria, insomnia, hypochondriases, disinclination for consecutive mental labor, severe and weakening attacks of sick headache and other analogous symptoms’ (p.218) made in the absence of evidence of ‘anaemia or of any other organic disease’ (p.218) suggested a typical case of neurasthenia. Later authors noted that, despite the diversity and, sometimes, severe nature of the symptoms, few if any objective signs of illness were apparent (Bloch, 1894) and sufferers were not obviously unhealthy (Ferrier, 1911).
Neurasthenia, Beard (1869) wrote, was most prominent in the civilised, intellectual communities, and more likely to affect the ‘nervous civilised man’ than the ‘hardy barbarian’ (p. 219), as it was associated with the ‘brain work’ of civilised society. Indeed, he viewed neurasthenia as part of the price paid for the continued progress and refinement of society. He noted that hereditary factors appeared to influence individual vulnerability to the development of neurasthenia, which may be provoked by physical and/or mental stressors such as acute or chronic illness, bereavement, business or family cares, childbirth, abortion, sexual excesses, substance abuse, ‘civilised starvation’ (p. 218) and sudden retirement from business (Beard, 1869).

Although Beard is credited as being the originator of the diagnosis, his contribution was, of course, not made in a vacuum, and he owed much to scientists who went before him (Demitrack & Abbey, 1996; Wessely, Hotopf & Sharpe, 1998). For instance, more than a century before Beard wrote, Sir Richard Manningham described the ‘febricula’ (little fever) in which sufferers complained of great lassitude and weariness all over the body, listlessness, transient chills and pain, and were ‘a little delirious and forgetful’ (discussed in Demitrack & Abbey, 1996). In fact, if Beard was the Charles Darwin (a comparison he made himself) of the disorder that he was later to refer to as the ‘Central Africa’ of medicine (Beard, 1880), then its Alfred Russell Wallace was a psychiatrist named E.H. Van Deusen. Almost simultaneous with Beard’s (1869) publication, Van Deusen, a psychiatrist working in the rural areas of Michigan, independently coined the term neurasthenia, and published his own description of it (Van Deusen, 1869).
Nevertheless, it was the particular combination of factors associated with Beard and his patients that resulted in the swift popularisation of the diagnosis, especially among the higher echelons of American and Western European Society at the time. Beard's social and professional status and, perhaps more significantly, the considerable social status of his patients, meant that his was a position of substantial popular and professional credibility. This was amplified by the fact that Beard promoted neurasthenia primarily as a malady of the 'better classes', rarely seen in the public wards of charity hospitals, and commonly striking down the best and brightest of individuals (Richmond, 1989). Crucially, he theorised an organic basis for the illness, utilising many of the exciting advances in medicine, physiology and physics that were occurring at the time (Wessely et al., 1998).

Following the failure of therapies that were typically available at the time, the treatment of choice, developed by another American neurologist, Weir Mitchell (1908), became the 'rest cure', which entailed rest, seclusion, massage, electricity and diet. This type of treatment was facilitated, generally at great expense, by having patients spend periods in private clinics or retreats, which subsequently flourished, particularly in Germany and the United States (Shorter, 1990).

While neurasthenia became an extremely common diagnosis in the decades following its original exposition, many in the medical profession remained sceptical of its proposed
organic basis. By the turn of the century, the continued lack of evidence for organicity, the impotence of medical treatments, including the rest cure, and the fact that it was becoming increasingly obvious that the illness was just as prevalent, if not more so, among the lower economic classes, had all contributed to produce a significant downturn of enthusiasm for the label amongst both doctors and patients (Wessely et al., 1998). Of particular importance in this respect, was the subsequent increase in the audibility and credibility of psychological models of neurasthenia, and the inevitable social stigma they brought with them (Demitrack & Abbey, 1996). Gradually from that point, use of the diagnosis fell into decline in general medical settings and, for the most part, it became the province of the then emerging discipline of psychiatry. A number of neurologists continued to diagnose and treat the condition into the middle decades of the 20th century, partly because some continued to believe in its neuropathological basis, and felt that they and their patients were justified in rejecting psychiatric models. For some doctors, however, continuing to affirm an organic basis for neurasthenia was probably also motivated by financial considerations, in that it provided justification for the treatment of patients who, for whatever reason, were unhappy with psychiatric explanations (Wessely, 1994).

As a result, while the term 'neurasthenia' gradually faded from use, it did not disappear entirely. Although it was dropped from the DSM-III (American Psychiatric Association, 1980), having been replaced by a number of alternative diagnoses, it remains as a
diagnosis in the current edition of the International Classification of Diseases (World Health Organisation, 1992), within the Mental and Behavioral diseases section.

**Unexplained Epidemics**

A second historical thread in the CFS tapestry relates to a number of reports of CFS-like illnesses occurring in epidemic form during the middle decades of this century. Although, in some important respects, characteristics of these illnesses differ from those of CFS as it is experienced today, these epidemics are seen by some as evidence for the existence of a specific medical entity that is directly related to CFS as it is currently defined (Jenkins, 1991; Sabin & Dawson, 1993). Other writers also see a clear link between these cases and CFS, but one that is mostly historical and supports a psychiatric rather than an infectious actiology (Wessely et al., 1998).

One review describes twelve epidemics which occurred between 1934 and 1961 in the US, Britain, Northern Europe, Australia and South Africa (Sabin & Dawson, 1993). Common symptoms were myalgia, mood disturbance, and a number of neurological symptoms, including impairment of memory and concentration, headaches, muscle weakness and paresthiasias. As was characteristic of neurasthenic patients, the number and severity of symptoms was almost always out of proportion to any laboratory findings or other objective signs (Demitrack & Abbey, 1996). Common features of the epidemics were that they often occurred in the context of wider polio epidemics or, at
least, fear of polio, and that women, health professionals and people of European
descent were substantially over-represented, while young children appeared immune. In
the hospitals where several of the outbreaks occurred, cases came almost exclusively
from staff members, especially nursing staff (Parish, 1978; Sabin & Dawson, 1993).

The two epidemics that have attracted most attention occurred in Los Angeles in 1934,
and in London in 1955. The Los Angeles outbreak involved 198 employees of the LA
County General Hospital, who were mainly medical staff. As it coincided with a
poliomyelitis epidemic, the illness was at first thought to be polio itself, despite clear
differences in presentation and course (Gilliam, 1938). Sufferers reported sudden onset,
often with general pain (which was rheumatic in nature), headaches, muscle tenderness
and weakness, fatigue, irritability, emotional lability and depression, sleep disturbance,
and memory and concentration deficits. Laboratory findings were almost always
unremarkable, nevertheless sufferers experienced considerable disability, particularly
during the acute phases of the illness. Gilliam (1938), after a thorough investigation of
the epidemic, concluded that there were good grounds for assuming that the majority of
cases resulted from infection with poliomyelitis virus and, although he noted that, in the
opinions of some observers, hysteria played an important role, he discounted it as being
a factor in a majority of cases.

The other significant outbreak occurred amongst the medical staff at the Royal Free
Hospital in London in 1955. Seventy staff members were admitted over a two-week
period with acute onset of viral-like illness with headache, sore throat, malaise, fatigue, vertigo and limb pains (The Medical Staff of the Royal Free Hospital, 1957). Over the next four months, 292 staff had contracted the illness, with 255 having to be admitted, many for over a month. Curiously, over the same period, only 12 of the hospital’s inpatients developed the symptom complex. As in the LA County Hospital outbreak, symptoms cycled through remission and relapse, emotional disturbance was prominent and laboratory tests were generally normal. The illness was particularly prevalent among young female resident nursing staff.

Some attempts have been made to provide an explanation of why these outbreaks were so confined to the medical staff of each hospital. Sabin and Dawson (1993) suggested that, during the era of the Los Angeles outbreak, health workers were likely to have been inoculated with pooled human serum as polio prophylaxis, and that this may have modified the polio infection or triggered another disorder. Ramsay (1978) reported evidence of reduced incidence of epidemic and sporadic CFS-like illnesses in sedentary individuals and suggested that patients may thus have been protected by their inactivity. On the other hand, a strong case was made for a largely hysterical origin for many of the cases during the Royal Free Hospital epidemic (McEvedy & Beard, 1970), and there is little doubt that at least a proportion of cases were emotionally based (Wessely, 1994). Both of the epidemics discussed occurred in a climate of high stress and fear over the threat of contracting polio. In contrast, in a very thorough review of these epidemics, Acheson (1959) argued that the clinical picture supports the view of a discrete clinical
entity of infectious origin, spread by personal contact. He suggested that, at minimum, it was reasonable to take the view that some true cases of staff members contracting poliomyelitis may have sparked a large number of hysterical responses among the other staff. Certainly, this would explain, to some degree, the fact that the illness seemed so selective with respect to who was affected, as well as some of the clinical findings (Jenkins, 1991). However, Acheson (1959) goes on to argue strongly against mass hysteria as a major factor in many of these outbreaks, citing, among other factors, the consistency of the symptoms and course of the illness despite the diversity of communities affected in the outbreaks. The arguments of Acheson (1959) show that, at least, an infectious cause cannot be dismissed, nor can the possibility that some other environmental factor played a role.

An editorial review of these epidemics, published in the Lancet in 1956, subsequently led to the diagnostic label ‘benign myalgic encephalomyelitis’ being suggested to refer to a possible new clinical entity that might account for many of these epidemic cases. The symptom criteria suggested were: symptoms and signs of CNS damage, protracted periods of muscle pain, emotional disturbance, normal cerebrospinal fluid analysis, reticuloendothelial system involvement, extended clinical course with frequent relapses, and an ultimately benign outcome.

For reasons that remain unclear, very few epidemics of this nature have occurred over the past few decades, an apparent outbreak near the shores of Lake Tahoe in California
and Nevada in the early 1990s being a significant exception (Buchwald et al., 1992).

Despite this, the link between these epidemics and modern CFS is evidenced by the fact that the term 'myalgic encephalomyclitis' (ME) persisted, particularly in the U.K., although its use was adapted somewhat to refer mainly to the many unexplained sporadic cases of fatiguing illness that were often associated with a precipitating infection of some kind. Through the 1970s and 1980s, ME and 'post-viral fatiguc' syndromes became the focus of renewed attention, which, ultimately, led to the development of the term 'chronic fatigue syndrome'. It is interesting to note in this context that the original criteria published in the Lancet editorial in 1956 for benign ME does not actually list fatiguc as a primary symptom.

**Post-Infectious Fatigue Syndromes**

While the remnants of neurasthenia, as a concept of the pathological loss of nervous strength, were fading in the years leading up to the Second World War, a new model was arising to perpetuate a strictly organic view of the disorder. Both Beard (1869) and Van Deusen (1869) had noted the prominent role of infectious illness in the precipitation of many cases of neurasthenia. However, the idea that infection was the basis for the chronic state of ill health associated with the disorder, rather than an initial trigger for other pathological processes, was not substantially explored until the 1930s. In 1934, Alice Evans published a description of an illness that closely mirrored the symptoms of neurasthenia, but which she suggested resulted from chronic infection with the brucella
species of bacteria (Evans, 1934). At the time, acute brucellosis was a relatively common complaint, transmitted mainly by cattle through infected dairy products and, less commonly, through skin lesions or inhalation (Morello, Mizer & Wilson, 1984). Noting that latent, localised brucella infections were able to persist in animals, Evans (1934) suggested that such infections may also occur in humans and could be responsible for the symptoms of many people who had been given the ‘dishonourable’ diagnosis of neurasthenia. The idea that at least a proportion of cases of neurasthenia may be due to a chronic underlying infection that was difficult to detect was a reasonable hypothesis, and attractive to those who eschewed psychiatric explanations for neurasthenia. However, the theory was intrinsically difficult to substantiate, and relied primarily on clinical anecdote and generalisation from animal models (Demitrack & Abbcy, 1996).

In 1951, Spink published findings of his work with more than 120 acute brucellosis patients. He followed 65 sufferers who had not been treated with antibiotics in order to investigate the factors that contributed to symptom persistence. He found that 30 of the original 65 non-treated subjects remained symptomatic to some extent after 1 year. Seventeen of these showed clear evidence of a continuing infective process. The other 13 chronically symptomatic patients showed no objective evidence of active infection and, of these, psychiatric illness was indicated in seven cases and compensation claims were thought to be involved in another two. Thus, in only four cases could no organic or psychiatric cause for symptom persistence be established (Spink, 1951). Spink (1951)
found a similar level of symptom persistence without clear organic cause in another 61 patients who were given antibiotic therapy.

Questions arising from Spink’s research were followed up over a number of years by researchers from Johns Hopkins University, commencing with the study of a group of employees from a laboratory where the analysis of brucella organisms was carried out (Cluff, Trever, Imboden & Canter, 1959). The researchers contacted 24 of an original 60 employees who had suffered from a clearly documented brucella infection, and conducted ongoing six monthly clinical and serologic assessments. One third of this group were completely asymptomatic within a year of their original infection and were regarded as recovered. Of the other 16 patients, six recovered within another year. Thus, ten patients remained symptomatic throughout the follow-up period. After detailed medical examination and thorough analysis of each patient’s case history, the researchers felt there was enough evidence to refute two of the three alternative hypotheses arising from Spink’s (1959) work. In comparing non-recovered and recovered patients, there was no evidence of chronic active brucella infection, nor was there evidence of any CNS damage resulting from the original infection (Cluff et al., 1959).

In a separate report, the researchers attempted to establish the validity of the third alternative; that the persistence of symptoms was due to psychological factors and, as such, was better described as neurasthenia or a psychoneurosis (Imboden, Canter, Cluff
& Trever, 1959). Assessments of psychological, cognitive and perceptual-motor functioning were made for all 24 patients, using a blindly scored test battery, incorporating the Wechsler Adult Intelligence Scale (WAIS), the Bender Visual Motor Gestalt test and the Minnesota Multiphasic Inventory (MMPI). An unblinded psychiatric interview was also carried out. Results indicated no differences in intellectual or psychomotor functioning between any of the groups. On the other hand, the two chronic groups (chronic-recovered and chronic non-recovered) scored higher on indicators of psychological impairment, such as the MMPI scales of psychasthenia and depression, as well as on a combination of scales 1-3 (hypochondriasis, depression and hysteria) that the authors devised as a ‘neurotic index’. The psychiatrist who conducted formal psychiatric interviews indicated that the chronic non-recovered group were more resistant to discussion of personal issues than either of the other two groups, and were more likely to attribute symptoms to organic factors associated with the original infection. Biographical assessment of all patients indicated traumatic childhood events in 11 of the 16 patients in the chronic-recovered and non-recovered groups, compared to only two of the eight in the acute-recovered group (Imboden et al., 1959). Further, 11 of the 16 patients in the chronic groups experienced significant stress in the year preceding their infection, compared to none of the eight acute recovered patients (Imboden et al., 1959).

While the differences between the groups on psychological measures were impressive and led the researchers to conclude that chronic brucellosis was, essentially, an
emotional disorder, some caution is warranted. First, psychological assessments were made after the patients in the chronic groups had been ill for an extended period. The impact of the illness itself upon psychological profiles needs to be considered. Second, many of the scales on the MMPI that were elevated contain items that ascertain the presence of somatic symptoms and, as such, higher scores on these scales may not necessarily represent greater psychopathology in individuals with organic illness. This is especially true for the scales the authors used to calculate their neurotic index. Third, the potential for systematic bias in psychiatric interviews, when the interviewer is not blind to the status of the patient is clear, although often unavoidable, and patients themselves may place more emphasis on previous stressful events, given that they too may be searching for reasons for their continued state of ill health.

Nevertheless, later prospective studies that were designed to overcome these methodological issues, and which used much larger sampling frames, offer strong support for the central role of psychological factors in prolonged recovery from infectious illness. Some of these studies will be discussed in later sections, however, it is appropriate here to outline the results of the prospective study carried out by the Johns Hopkins group as a follow-up to their study reviewed immediately above. The researchers anticipated an impending flu epidemic in 1957, and carried out prospective psychological assessments on 600 employees at a US Army base in Maryland (Imboden, Canter & Cluff, 1961).
Employees who reported to the medical facility with symptoms underwent clinical assessment, which included laboratory testing, and were required to return for further assessment between 3-6 weeks later. Of the 26 employees who contracted influenza that winter, 14 had recovered completely by the 3-6 week check up, while 12 reported persisting symptoms such as: fatigue, headaches, sleep disturbance, and depressed mood. These symptoms were similar to those reported by the chronic brucellosis patients in the earlier study (Cluff et al., 1959). In comparing the recovered versus the persistently symptomatic group, there were no differences in the symptoms reported during the acute phase of the illness, nor were there any systematic differences regarding laboratory results at onset or at follow-up. However, depression and morale loss scores on the MMPI, and total score on the Cornell Medical Inventory, taken at least 3 months prior to the infectious illness, were significantly higher in the persistently symptomatic group. The authors suggested that the onset of infectious illness might trigger the development of depressive symptoms (including fatigue, and vague somatic concerns) during the illness, and that these might obscure the endpoint of the physical illness from the patient and their treating physician (Imboden et al., 1961). It follows that such a scenario could also engender a pattern of attribution in which symptoms that are related to depression are mistakenly ascribed solely and directly to the infection. While this study used only a short follow-up, later investigations carried out over longer periods produced similar results (Wessely, et al., 1995).
Chronic brucellosis virtually disappeared as a diagnostic entity following the publication of these influential studies, in a manner that Wessely et al. (1998) noted as parallel to the way in which neurasthenia declined from favour once psychological factors were strongly implicated in its aetiology. The decline in interest in these syndromes is in large part due to the Cartesian separation of the causes of illness into physiological and psychological, a distinction which is synonymous with ‘real and unreal’ in the minds of many in the professional and general communities alike. Thus, illnesses that are found to be related to psychological phenomena are invalidated to a large extent in the eyes of many in the medical profession and the public. As a result, some important questions that pertain to the relationship between psychological and physiological states are left largely unanswered. The Cartesian approach to understanding syndromes such as CFS has been identified as a major impediment to progress in the area (Demitrack & Abbey, 1996). In this context, it should be noted that, in each of the studies that demonstrated significant psychiatric involvement in the perpetuation of symptoms, there were a small group of sufferers whose illness was not attributable to either organic or psychological factors. As such, even if the loss of interest in functional somatic syndromes that occurs when psychological factors are implicated was justified on other grounds, some cases of unexplained illness are still overlooked. This problem becomes more significant when one considers more recent epidemiological studies that indicate that cases of chronic, disabling fatigue are substantially more common than cases of the more stringently defined chronic fatigue syndrome (Buchwald et al., 1995).
The Merging of Post-Infectious Fatigue and Epidemic Myalgic Encephalomyelitis

The drop in public and professional interest in chronic brucellosis did not mean that cases of prolonged recovery from infectious illness or other life events disappeared, or even significantly declined. And, of course, some interest in these syndromes remained, especially among those who continued to believe that an infectious agent or agents were responsible. The next stage in the process that eventually led to the development of the diagnostic entity ‘chronic fatigue syndrome’, involved the merging of interest in epidemic ME with that of sporadic post-infectious fatigue syndromes (Wessely et al., 1998).

A symposium was held at the Royal Society of Medicine in 1978 in order to discuss ME and promote a concerted research strategy (Jenkins, 1991). To some extent, this meeting arose from a ME study group that had been set up two years earlier, which was comprised, in part, of some of the medical staff who had been involved with, or directly affected by, the Royal Free outbreak more than 20 years previously (Wessely et al., 1998). This group was of the opinion that the 1955 epidemic involved an organic disease, complicated by encephalomyelitis and with myalgia as a dominant feature (Compston, 1978). The meeting reaffirmed the nomenclature ‘myalgic encephalomyelitis’, noting that the addition of the word ‘benign’ was misleading with respect to the impact the disease had on sufferers (Jenkins, 1991). A substantial amount of evidence for an organic basis for ME was presented.
However, the lack of epidemic cases over the previous two decades meant that sporadic cases became the central focus of further investigation and, as such, these cases came to be more commonly labelled as ME, at least in the UK and Canada. Wessely et al. (1998) noted that this change in focus led to a profound but largely unnoticed change in the character of the illness. While epidemic ME was contagious, acute, accompanied by paralysis and neurological signs, sporadic ME, or CFS, as it was to become known, is non-contagious, chronic, fatiguing and free of neurological signs. Wessely et al. (1998) use this to demonstrate that the links between epidemic ME and the currently defined CFS are mostly historical, and that epidemic cases would not qualify for the diagnosis of CFS.

**Chronic Fatigue Syndrome**

The outcome of the 1978 meeting may have served to fortify and unite what were, until then, pockets of interest in the syndrome in the scientific and general communities. However, the real resurgence in interest in chronic fatigue states did not occur until the early to mid 1980s, sparked by three independent reports of a number of cases of persisting illness with the same symptom profile as that associated with sporadic ME (Jones et al., 1985; Straus et al., 1985; Tobi et al., 1982). The common feature of these studies that excited so much scientific and public interest were parallel findings of subtle immunological changes in patients and, in particular, abnormal antibody responses to
Epstein-Barr Virus (EBV). This, combined with the fact that the chronic illness had
developed following episodes of acute infectious mononucleosis in a large proportion of
these patients, led to the hypothesis that chronic EBV infection was responsible for the
protracted illness. The diagnosis of ‘chronic active Epstein-Barr virus’ or ‘chronic
mononucleosis’ became popular, and despite the fact that evidence was quickly accruing
to clearly refute the importance of EBV in most people diagnosed with the disorder
(Buchwald, Sullivan & Komoroff, 1987; Holmes et al., 1987), the combined forces of
clinical and research interests, lobbying by patient support groups, and media exposure,

In 1987, the Centers for Disease Control (CDC) in Atlanta commissioned a working
group to address a number of important concerns that had arisen out of the debate
surrounding chronic active EBV infection (Holmes, et al., 1988). Primarily, these
concerns were that: 1. The diagnosis of chronic active EBV infection was commonly
being made using inconsistent and often unreliable criteria; 2. Strong evidence against
the role of EBV in most cases meant that the diagnosis resulted in many other potential
factors being overlooked; 3. The use of a name that implies a specific causal agent in
such circumstances was inappropriate, and; 4. The nonspecific nature of symptoms and
lack of diagnostic test meant that researchers were using varying case definitions,
rendering direct comparisons between studies extremely difficult and impeding a
coordinated effort to understand the syndrome (Holmes et al., 1988).
The working group was comprised of scientists and clinicians from the USA, several of whom had made significant contributions to the area over the preceding years. Their goals were, firstly; to devise an appropriate name for the condition that did not attribute cause to any particular agent, infectious or otherwise, and secondly; to develop a consensus based set of operational criteria for the disorder. The name the working group agreed upon was ‘chronic fatigue syndrome’ (Holmes et al., 1988). The criteria put forward are presented in Figure 1.1. Fundamentally, a case of CFS required prolonged, disabling fatigue of greater than 6 months duration, accompanied by a number of specific symptoms and/or signs. Importantly, all possible clinical conditions (medical and psychiatric) had to be excluded before the diagnosis could be made. This involved appropriate physical and mental examinations, history taking and a prescribed minimum battery of laboratory tests.

In the same year, Australian researchers also published formal criteria to define the condition, which they had also called ‘chronic fatigue syndrome’ (Lloyd, Wakefield, Boughton & Dwyer, 1988). While the essential criteria of prolonged unexplained fatigue was the same as in the CDC definition, either neuropsychiatric dysfunction or abnormal cell mediated immunity also had to be present in order for patients to be classified as CFS sufferers. A list of secondary symptoms similar in many respect to the CDC definition were also provided, but only as supporting criteria, that is, their presence was not essential for the diagnosis (Lloyd et al., 1988). The inclusion of the altered cell-mediated immunity condition was controversial, as evidence of this being a reliable
marker for the disorder was inconclusive, and a later definition published by the same group (Lloyd, Hickie, Boughton, Spencer & Wakefield, 1990) dropped this criterion.

In 1991, a British group also convened and produced their own set of criteria for CFS (Sharpe et al., 1991), which sought to improve upon aspects of the CDC definition that were seen as either controversial or absent. The British criteria were similar to the Australian definition in that premorbid or concurrent psychiatric diagnoses were not a condition for exclusion, apart from those which were clearly confounding, such as psychotic, bipolar, substance abuse and eating disorders. Also, like the Australian definition, the British criteria placed far less emphasis on the presence of secondary somatic symptoms than the CDC definition had done. Unlike either of the previous definitions, the British group made several recommendations regarding research methodology and criteria for comparison of studies in the area.

One of the original aims of the CDC was to produce criteria that identified a relatively homogenous group of ‘pure’ CFS sufferers, so as to increase the likelihood that underlying pathological dysfunctions in these patients would be found, if they existed (Holmes et al., 1988). This was the major reason for the central differences between the CDC criteria and that of the Australian and British groups with respect to the exclusion of patients with psychiatric illness and the extensive secondary and physical symptom requirements. However, over a relatively short period, it became clear that the CDC criteria were not working as intended in several respects.
MAJOR CRITERIA

1. New onset of persistent or relapsing, debilitating fatigue in a person who has no previous history of similar symptoms, that does not resolve with bed rest, and that is severe enough to reduce or impair average daily activity below 50% of that patient’s premorbid activity level for a period of six months.

2. Other clinical conditions that may produce similar symptoms must be excluded by thorough evaluation, based on history, physical examination, and appropriate laboratory findings.

SYMPTOM CRITERIA

1. Mild Fever
2. Sore throat
3. Painful lymph nodes
4. Unexplained generalised muscle weakness
5. Muscle discomfort or myalgia
6. Post-exertional fatigue lasting more than 24 hours
7. Generalised headaches of new type, severity or pattern
8. Migratory arthralgia
9. Neuropsychologic complaints
10. Sleep disturbance
11. Initial onset of symptom complex over days or hours

PHYSICAL CRITERIA

1. Low grade fever (oral 37.6-38.6, rectal 37.8-38.8)
2. Non-exudative pharyngitis
3. Palpable anterior or posterior cervical or axillary lymph nodes.

Figure 1.1 The original CDC case definition for CFS (Holmes et al., 1988). CFS cases had to fulfil both of the major criteria and EITHER 8 of the symptom criteria OR 6 symptom criteria plus 2 physical criteria, with all known medical and psychiatric causes excluded.
Firstly, Katon and Russo (1992) demonstrated that CFS patients with higher numbers of somatic symptoms tended to have a higher incidence of psychiatric disorder. They argued that the inclusion of extensive somatic symptom criteria therefore actually increased the likelihood of including patients with psychiatric disorder. This is likely to increase the heterogeneity of the population under study (Hickie, Lloyd, Hadzi-Pavlovic & Parker, 1995), which is opposite to the intended purpose of the requirement of multiple somatic symptoms. Secondly, disagreement about the exclusion of cases on the basis of psychiatric diagnoses such as depression and anxiety, which are very common in CFS patients (Abbey, 1996), coupled with the fact that the CDC criteria were so stringent and, therefore, difficult to comply with, meant that they were being inconsistently applied (Fukuda et al., 1994). Thirdly, the CDC’s own research indicated that the criteria did not define a distinct subset of patients in any clinical or demographic sense (Fukuda et al., 1994).

The result of these and other problems associated with the original case definition (Holmes et al., 1988), was a modification of the criteria in 1992 (Schlueterberg et al., 1992) and their complete revision in 1994 (Fukuda et al., 1994). Major changes between the original and the 1994 criteria, which are summarised in Figure 1.2, were a substantial reduction in the number of unexplained medical symptoms necessary from eight to four, and the removal of the physical symptom criteria altogether. The rather subjective and difficult to establish criterion of a 50% reduction in activity levels was replaced by the requirement of ‘substantial reduction’ in activity from premorbid levels.
MAJOR CRITERIA

Clinically evaluated, unexplained persistent or relapsing chronic fatigue that is:

1. Of new or definite onset (i.e., not lifelong)
2. Is not the result of ongoing exertion
3. Is not substantially alleviated by rest
4. Results in substantial reduction in previous levels of occupational, educational, social, or personal activities.

SYMPTOM CRITERIA

The concurrent occurrence of four or more of the following symptoms

1. substantial impairment in short-term memory or concentration;
2. sore throat;
3. tender lymph nodes;
4. muscle pain;
5. multi-joint pain without swelling or redness;
6. headaches of a new type, pattern, or severity;
7. unrefreshing sleep; and
8. post-exertional malaise lasting more than 24 hours.

These symptoms must have persisted or recurred during 6 or more consecutive months of illness and must not have predated the fatigue.

EXCLUSIONARY CRITERIA

1. Any active medical condition that may explain the presence of chronic fatigue, such as untreated hypothyroidism, sleep apnoea and narcolepsy, and iatrogenic conditions such as side effects of medication.

2. Diagnosable illnesses that may relapse or may not have completely resolved during treatment, if the persistence of such a condition could explain the presence of chronic fatigue, and if it cannot be clearly established that the original condition has completely resolved with treatment.

3. Any past or current diagnosis of a major depressive disorder with psychotic or melancholic features; bipolar affective disorders; schizophrenia of any subtype; delusional disorders of any subtype; dementias of any subtype; anorexia nervosa; or bulimia nervosa.

4. Alcohol or other substance abuse, occurring within 2 years of the onset of chronic fatigue and any time afterwards.

5. Severe obesity as defined by a body mass index [body mass index = weight in kilograms / (height in meters)^2] equal to or greater than 45.

6. Any unexplained abnormality detected on examination or other testing that strongly suggests an exclusionary condition must be resolved before attempting further classification.

Figure 1.2 The 1994 CDC revised case criteria for CFS (Fukuda et al., 1994)
The criteria also defined ‘idiopathic chronic fatigue’ as a category for patients whose chronic fatigue is not explained by any diagnosable disorder, but who do not meet the case definition for CFS (Fukuda et al., 1994).

While the original CDC criteria were based on consensus within the USA, the 1994 case definition represented an international consensus, as the revision panel included several members from each of the Australian and British teams that had developed definitions of their own. As such, they have facilitated a more cooperative and efficient international effort to understand the syndrome. It is expected that the criteria will remain subject to iterative changes as this process produces more information about CFS, or until a diagnostic test is developed (Fukuda, 1997).

Conclusions

One hundred and twenty five years had passed between Beard’s original publication of Neurasthenia as a diagnostic entity (Beard, 1869) and the development of an international consensus on the definition of CFS (Fukuda et al., 1994). Perusing the definitions side by side, one might be excused for concluding that, in the intervening century and a quarter, the most significant change from Beard’s original position has been in the renaming of the disorder itself. Certainly, progress in the area has in no sense kept pace with developments in many other areas of scientific study, medical or otherwise. Primarily, this is because many aspects of the illness, such as its heterogeneity, its overlap with many other disorders and, most importantly, the lack of
objective markers, present particularly difficult challenges to scientific investigation. But the elusiveness of the construct with respect to scientific scrutiny has also interacted with cultural factors, and with the inherently dualistic but patently invalid separation of the concepts of physical and mental illness, and the stigma associated with the latter in public and professional circles. Thus, the condition variously named ‘febricula’, ‘neurasthenia’, ‘chronic brucellosis’, ‘myalgic encephalomyelitis’, ‘post-viral fatigue syndrome’, ‘chronic active Epstein-Barr virus infection’ and, presently, ‘chronic fatigue syndrome’ has cycled through phases of interest, which have been characterised by periods of intense attention, as potential organic causes are reported to refute psychiatric models, followed by stages of ignominy as those potential organic models fail to receive empirical support and the syndrome is dishonourably discharged back to the psychiatric realm. Generally, these phases have been separated by periods of relative anonymity, until the next exciting organic theory gains a foothold.

As such, an appreciation of the history of the construct is vital to enable researchers and clinicians to contextualise the sometimes nebulous and often conflicting issues associated with working in the area. The attempt by the CDC to bring structure to the international effort to understand the syndrome, and the recent move away from Cartesian conceptualisations of the disorder that has been initiated by influential members of the CFS research community (eg. Demitrack & Abbey, 1996; Hickie, Lloyd & Wakefield, 1995; Sharpe, 1998; Wessely et al., 1998), provides a strong hope that the historical cycle of interest-disdain-disinterest in the disorder will be broken and replaced with a sustained effort to understand the condition.
CHAPTER 2

PREVALENCE, ASSOCIATIONS, COURSE AND IMPACT
The discussion in the previous chapter focussed on establishing an understanding of the scientific and social forces that have shaped the way that CFS is conceptualised today. The aim of this chapter is to provide a perspective on the magnitude of the problem that CFS currently represents, both in terms of its impact on individual sufferers and the community as a whole. The discussion commences with a brief review of the epidemiology of fatigue in general, which is followed by a review of the literature that has sought to estimate prevalence rates for CFS specifically. Reports that CFS is particularly prominent in specific demographic subgroups will be evaluated. Finally, the typical course of the illness will be outlined, as will estimates of its social and economic impacts.

**General Fatigue: Epidemiology and Associations**

Fatigue is a very common complaint, even in the general community (Chen, 1986; Loge, Ekeberg & Kaasa, 1998). A recent Norwegian survey of 3,500 adults who were selected at random from a national population registry found that 22% of respondents reported suffering from substantial fatigue, with half of them having done so for longer than 6 months (Loge et al., 1998). Studies in other countries have reported similar findings (Kroenke & Price, 1993; Schepank, 1987). Estimates vary on the prevalence of fatigue in primary care settings, depending on the sampling technique and the means of measurement, but a number of reports have indicated that significant and prolonged
fatigue is reported by between 21% and 27% of general patients (Bates et al., 1993; Buchwald et al., 1987; Hickie et al., 1996; Kroenke, Wood, Mangelsdorff, Meier & Powell, 1988).

Several studies have noted a higher incidence of fatigue in women than in men (Fukuda et al., 1997; Hickie et al., 1996; Kroenke et al., 1988; Loge et al., 1998). Although Loge et al. (1998) reported a relatively small gender difference, with 10% of men reporting substantial fatigue, compared with 13% of women, in the general population, larger differences have been reported in primary care (19% in men vs 28% in women: Kroenke et al. (1988)). Despite these variations in magnitude, the general finding appears reliable (Chen, 1986). It is unclear why females would report more fatigue than males, although there have been several suggestions. Lawrie and Pelosi (1995) posited that lower levels of physical fitness, reproductive factors, or combined occupational and domestic responsibilities might contribute to the difference. Alternatively, the results may reflect an increased preparedness of women to present to general practitioners. While this last point may explain higher prevalence rates for women in primary care, they can not account for the same findings in population based studies. Another possibility, raised by Chen (1986), is that higher prevalence of fatigue amongst women is due to higher rates of psychological symptoms. However, while high scores on depression scales have been associated with high scores on fatigue scales (Pawlikowska et al., 1994), and fatigue is associated with depressive and anxiety disorders (American Psychiatric Association,
1994), studies that have controlled for these do not remove the gender differences completely (Hagnell, Grasbeck, Ojesjo & Otterbeck, 1993).

A relationship between fatigue and aging is less apparent, except, perhaps, at the extreme ends of the age continuum. Wessely et al. (1998) reviewed a number of studies that suggest that fatigue in children is far less common than it is in adolescents and adults. Population and primary care studies demonstrate that the prevalence of fatigue is quite stable across adults of different age ranges (Loge et al., 1998; Hickie et al., 1996). Although Loge et al. (1998) reported significant positive correlations between fatigue and age in both men and women, these differences were only apparent once people were over 60 years of age. Steele et al. (1998) reported significantly higher levels of explainable fatigue in people over 60 years of age, while levels of unexplained fatigue in this group were similar to younger adults. This suggests that increased fatigue reported in older persons is likely to be related to increases in general health problems associated with aging.

Lower socio-economic status (SES) has been associated with higher levels of fatigue in population and primary care based studies (Hickie et al., 1996; Lawrie & Pelosi, 1995; Steele et al., 1998), although some studies have found no such relationship (Fukuda et al., 1997). A likely contributor to increased levels of fatigue in lower socioeconomic strata is increased social adversity (Wessely et al., 1998).
Epidemiology of CFS

While fatigue, and even chronic fatigue are quite common in the general community, chronic fatigue syndrome is much less so. The first formal population based epidemiological investigation of CFS, which is the only study carried out in an Australian community, was conducted by Lloyd et al. (1990) in the Richmond Valley region of New South Wales. The investigators relied upon notification of potential CFS cases by medical practitioners in the catchment area, and the cases were followed up with a screening questionnaire and thorough medical and psychiatric evaluation. Using the Australian criteria (Lloyd et al., 1990) the investigators calculated a point prevalence rate of 37 cases per 100,000 (0.037%). As discussed in the previous section, the Australian criteria (Lloyd et al., 1990) were somewhat less stringent than either the CDC criteria at the time (Holmes et al., 1988) or the current CDC definition (Fukuda et al., 1994). As such, the prevalence rate obtained may be somewhat higher than would have been the case had the CDC criteria been used.

A later study that used the Holmes et al. (1988) criteria to identify cases (Gunn, Connell & Randall, 1992) arrived at a much lower rate of between 2.0 and 7.3 cases per 100,000. However, this study also used physician referral as the source of cases, and several problems have been identified with epidemiological studies that obtain their samples in this way. First, sampling may be biased by the fact that, in general, people who are of low socioeconomic status have less access to the health-care system (Mechanic, 1983), although this may be less of a problem in countries such as Australia, where health care
is more freely available than it is in the US. Even so, people from lower SES backgrounds, who are also more likely to be educationally disadvantaged, may be less likely to search widely to obtain an appropriate diagnosis. While this may lead to the illness being diagnosed more often in people from the middle and upper social classes (Wessely et al., 1998) and feed the common misperception of CFS as primarily existing within this population (hence the term ‘Yuppie Flu’), there is no strong evidence of higher prevalence rates in this group compared to others (Wessely, 1995). Reports of a higher prevalence of CFS-like illness in lower income groups (Steele et al., 1998) are also problematic and inconclusive and, overall, there is no strong evidence of a link between SES and the incidence of CFS.

A second, more significant problem associated with physician referral, however, and one that is specific to studies of CFS, is that a proportion of medical practitioners do not perceive the condition as a valid diagnostic entity and, subsequently, will not refer potential cases (Jason et al., 1995a). This being the case, the use of physician referral as the method of case notification in the Lloyd et al. (1990) and Gunn et al. (1992) studies may have led to an underestimation of prevalence rates, as a number of true cases of CFS may not have come to the investigators’ attention. Also, the 1994 CDC criteria (Fukuda et al., 1994) are less stringent than those outlined in 1988 (Holmes et al., 1988), and similar, in some respects, to the Australian criteria in that co-morbid psychiatric diagnoses such as depression or anxiety are no longer cause for exclusion from the diagnosis of CFS.
Using methodology that was designed to overcome these issues, Jason et al. (1995b) accessed a community sample of 1,031 people at random via telephone interviews conducted across three different geographic locales in the greater Chicago area. The investigators reported a point-prevalence estimate for CFS of two cases per 1000 (0.2%), however, only one of the two cases diagnosed as CFS met the CDC criteria (Holmes et al., 1988) while the second met the less stringent British (Sharpe et al., 1991) and Australian (Lloyd et al., 1990) criteria. Given that the stringency of the original CDC criteria (Holmes et al., 1988) was relaxed in the 1994 revision (Fukuda et al., 1994), it may be that this second case would have also been included if this definition had been used.

Buchwald et al. (1995) randomly selected 4,000 members of a health cooperative in order to estimate the point prevalence of CFS and of unexplained chronic fatigue. Respondents were identified as potential CFS cases if they indicated that they had been unusually fatigued, either constantly or repeatedly for at least the previous six months, and that the fatigue had forced them to cut their work or home responsibilities by at least half. Cases were dismissed if they subsequently reported any medical or psychiatric condition that could account for the fatigue. Those respondents who denied any of these potential causes for their fatigue, but whose medical records indicated unreported, unrecognised or incompletely evaluated medical or psychiatric conditions, or regular use of medications or other substances that might produce chronic fatigue were also
excluded. Although 590 of the 3066 people who responded to the survey indicated that they suffered from chronic fatigue, 388 of these had medical and/or psychiatric conditions that precluded the diagnosis of CFS. Of the 202 people remaining, 128 either refused to participate further in the study or were unable to be contacted. This left 74 possible cases of CFS, and these respondents were thoroughly medically and psychiatrically evaluated according to the CDC criteria (Fukuda et al., 1994).

Of these 74 potential cases of CFS, only 3 were assessed as clearly meeting the original CDC criteria (Holmes et al., 1988), and the remaining 71 participants were classified as suffering chronic fatigue alone. Point prevalence estimates were estimated on the basis of different assumptions about the likely presence of chronic fatigue and CFS in the original 934 nonrespondents, and the 202 nonparticipants. The very conservative assumption, that none of the nonrespondents or nonparticipants suffered either chronic fatigue alone or CFS, resulted in community point prevalence rates of 1775 cases per 100,000 of chronic fatigue alone (1.78%), and 75 cases of CFS (0.08%). Estimates based on the assumption that rates among nonrespondents and nonparticipants were similar to those found for study participants, resulted in rates of 6321 cases per 100,000 (6.32%) of chronic fatigue alone, and 267 cases (0.27%) of CFS (Buchwald et al., 1995). The strength of these estimates is that, although they come from a population of people who could afford health insurance, they are derived from a large community-based sample, using stringent methodology. It is possible that the stringency of the exclusionary criteria applied in the early stages of the identification of potential cases led to some
CFS sufferers being overlooked due to the bluntness of the methodology that was necessary to deal with such a large sample. More significantly, use of the original CDC definition will have meant that cases that would now be diagnosed as CFS using the less exclusionary 1994 criteria (Fukuda et al., 1994) may have been overlooked. As such, these figures are possibly an underestimate of the true population prevalence rate of CFS as it is currently defined.

The term ‘CFS-like’ has been used in recent times to refer to cases that appear to be CFS but, generally for practical reasons, have been incompletely evaluated according to the CDC criteria (Fukuda et al., 1994). Generally, this means that the required laboratory testing has not been completed, although review of patients’ medical records is often carried out. Steele et al. (1998) reported an epidemiological telephone survey of 8004 San Francisco households that collected fatigue and demographic information on almost 17,000 residents. Using the 1994 case definitions (Fukuda et al., 1994), they reported prevalence rates of 0.2% for CFS-like illness and 1.8% for Idiopathic chronic fatigue-like illness. Another study in Michigan (Fukuda et al., 1997) reported household rates of CFS-like illness of 2.8%. Due to design limitations, prevalence among individual residents was unable to be calculated (Fukuda et al., 1997).

Other studies, using different criteria or based in specific populations, such as primary care patients, arrive at different estimates. Lawrie and Pelosi (1995) conducted a population-based survey in Scotland, using the British criteria. Not surprisingly,
considering the less exclusionary nature of those criteria, the authors reported a
community prevalence rate of 0.56%, more than twice that of the recent estimates based
on CDC definitions. A study of CFS prevalence in British primary care found that 2.6%
of attenders met the 1994 CDC criteria (Wessely, Chalder Hirsch Wallace & Wright,
1997), although this figure dropped substantially (0.5%) when patients whose primary
disability could be associated with psychological diagnoses were removed.

**Demographic Associations**

Most of the data linking CFS with demographic factors such as female gender, middle
and upper social class and health professionals has been derived, at worst, from anecdotal
and, at best, from studies of people presenting to primary or higher level care. While
anecdotal evidence is clearly unreliable, studies of patients who have sought and
received care are also problematic in that: 1. compared to men, women are more likely
to seek medical attention (Verbrugge, 1985); 2. access to medical facilities is more
available to those of higher SES and; 3. members of certain professions, including
teachers and health professionals, tend to be over-represented in those populations
(Wessely et al., 1998).

It is difficult to draw conclusions regarding the demographic profile of people diagnosed
with CFS. Partly, this is due to the fact that the relative rarity of CFS means that in
samples of several thousands of people, relatively few cases of CFS are detected,
limiting the conclusions that can be drawn. For example, in the two epidemiologic studies cited in the previous section in which complete assessment of cases was carried out, a combined total of 5 CFS cases were identified from more than 5000 people surveyed (Buchwald et al., 1995; Jason et al., 1995b).

One man and one woman made up the sample of CFS sufferers identified by Jason et al. (1995b). In the Buchwald et al. (1995) study, there were two women and one man diagnosed with CFS. Other studies, where the criteria are less stringent or less completely assessed, tend to indicate a higher proportion of women meeting the diagnosis (Fukuda et al., 1997; Lloyd et al., 1990; Steele et al., 1998), although Lawrie and Pelosi (1995) found equal representation across gender in their respondents who met the British criteria for CFS. Thus, although the evidence of higher rates of general fatigue in women is reasonably strong, as yet there are not enough data to be able to determine whether gender differences exist in CFS.

With respect to social class, there is no evidence to support popularly held beliefs linking CFS with higher SES. Several population based studies have found no relationship between SES and CFS (Fukuda et al., 1997; Lloyd et al., 1990), others attribute differences to selection bias (Lawrie, Manders, Geddes & Pelosi, 1997; Lawrie & Pelosi, 1995), while some find that lower SES is actually more likely to be a risk factor (Steele et al., 1998). Evidence for higher rates of CFS diagnoses in health professionals is also conflicting. Lawrie and Pelosi (1995) found that health professionals were not over-represented in any of the fatigue categories from their
population study, which was admittedly small. In substantial contrast to this finding, Jason et al. (1998) surveyed 3,400 nurses from 2 nursing associations in the USA, and calculated a prevalence rate for CFS of 1088 cases per 100,000, which is between 5 and 10 times the rates reported for the general population. These authors suggested that increased exposure to infections, stressful work circumstances and disruption to biological rhythms due to shift work could contribute to higher rates of CFS amongst nurses. However, low response rates to their initial questionnaire, response bias, and the fact that CFS criteria were incompletely assessed (medical records were used to exclude alternative diagnoses in place of laboratory screening), may have led to an inflation of true prevalence rates amongst the population studied. Even so, considering the substantial increase over normal prevalence figures, a relationship between CFS and occupation cannot be completely dismissed. As such, the question of whether health-care workers are at greater risk that the general population is an area requiring further research.

There are a number of other associations or risk factors that have been indicated, such as psychological disorder, infections and stress. These will be dealt with in Chapter 3.

**Course and Impact**

Studies examining outcome in CFS suggest that complete recovery, at least in the shorter term, is relatively uncommon. Wilson et al. (1994) conducted follow up assessments with 103 CFS patients who had been involved in treatment trials, on
average, 3.2 years earlier. While 65 respondents reported improvement in their condition, only six indicated complete recovery. A substantial proportion of sufferers remained significantly functionally impaired. Vercoulen et al. (1996) reported even poorer recovery rates in their sample of nearly 300 sufferers, with only 17% reporting improvement and 3% recovered after 18 months. Of 177 CFS cases followed up by Sharpe, Hawton, Seagroatt & Pasvol (1992) after four years, two thirds had experienced some improvement in their illness, but only 13% had recovered.

While these studies are all from tertiary care samples and, therefore, may be reflective of CFS in its most severe or entrenched form, results from primary care studies are not substantially better. Kroenke et al. (1988) found that only 28% of their patients had experienced any improvement in their condition after one year, with 50% unchanged and 22% reporting an exacerbation. However, these figures may offer a picture of CFS that is distorted towards the negative, as many people are known to recover in the earlier stages of the illness and escape the attention of such studies (Levine, 1996). Clearly, further research is necessary using population samples and longer follow-up intervals. At this stage, however, it is clear that many people who are diagnosed with CFS experience protracted periods of functional disability of several years duration and that, while most people improve over time, a substantial proportion are unlikely to regain premorbid levels of functioning.
Factors that have been associated with poorer outcome include older age (Bombardier & Buchwald, 1995; Clark et al., 1995; Kroenke et al., 1988), history of psychiatric disorder (Bombardier & Buchwald, 1995; Clark et al., 1995; Sharpe et al., 1992), more physical symptoms (Clark et al., 1995) or disability at original consultation (Kroenke et al., 1988), and attribution of symptoms to a physical cause (Sharpe et al., 1992; Vercoulen et al., 1996; Wilson et al., 1994).

CFS sufferers report a range of disability. Some are able to maintain full-time work, while others are extremely impaired and may not even be able to carry out basic self-care. Yeomans and Conway (1991) reported that 13% of the CFS sufferers in their sample were able to maintain full-time work, while 47% had lost their employment due to their illness. Several studies demonstrate that CFS leads to occupational, financial, domestic and social impairment that is similar or greater in extent to that associated with other chronic medical disorders (Anderson & Ferrans, 1997; Buchwald, Pearlman, Umali, Schmaling & Katon, 1996; Komaroff et al., 1996). Buchwald et al. (1987) found that 45% of their sample of CFS sufferers reported being periodically bedridden.

The professional and public scepticism surrounding the validity of the diagnosis of CFS has also been reported to have a major negative impact on the lives of sufferers. Komaroff and Buchwald (1991) found that a third of sufferers in their sample experienced strained relationships with family, friends and work-mates as a result of the lack of acceptance, disbelief or poor understanding of the illness. Ninety percent of this
group reported frequent feelings of isolation, alienation and inadequacy. Thomas English (1991), a physician who suffered from CFS, described how the sceptical, invalidating attitude of many in the medical profession towards the illness compounded the demoralisation he and many other sufferers felt in association with lost careers, homes, families, and cognitive skills.

Lloyd and Pender (1992) estimated the combined direct (diagnosis and treatment) and indirect (lost productivity) economic costs to the community for each case of CFS to be AUS$9,436 p.a.. This was calculated on the basis of 1988/89 cost of living figures. These figures were recently revised to $12,228 p.a. to reflect the increases in costs over time (Royal Australian College of Physicians, 1997). Based on reasonably conservative estimates of the prevalence of CFS in the community, the annual cost to the Australian economy was calculated to be more than $400,000,000 (Royal Australian College of Physicians, 1997).

Conclusions

Although the proportion of individuals who meet the stringent CDC diagnostic criteria for the diagnosis of CFS is relatively small, the cost to individuals and their communities is substantial. It should also be noted that these costs do not include those associated with the much larger percentage of individuals in the community who suffer from clinically significant fatigue but who do not qualify for the diagnosis of CFS. In this context, the continuing efforts expended upon the task of identifying the factors that
underpin CFS, as well as the development of appropriate treatment strategies are clearly justified. It is these efforts that are the subject of the following chapter.
CHAPTER 3

RESEARCH INTO THE AETIOLOGY AND PATHOPHYSIOLOGY OF CFS
The resurgence in interest in fatigue syndromes that was sparked in the early 1980s, and eventually led to the development of the consensus definition of CFS, has resulted in a substantial and sustained international research effort over the past 15 years. The efficiency of this effort has been somewhat compromised, largely due to the problems associated with the availability and/or the consistent application of a clear, appropriate case definition. Also, it has recently become clear that another significant factor contributing to the lack of progress in understanding the nature of CFS is that its heterogeneity, with respect to onset, clinical presentation and course, is apparently reflective of the likelihood that no single process is responsible for the disorder (Demitrack & Abbey, 1996; Wessely et al., 1998).

The following section will outline some of the major research directions taken in order to investigate the aetiology and underlying pathophysiology of the disorder. This will begin with an overview of the search for a common infective agent, the approach that dominated CFS research through the 1980s. The failure of this approach gave rise to two of the more dominant models of the early part of the 1990s. These models viewed CFS as either a psychiatric disorder or as a disturbance of immune regulation. More recently, the research focus has shifted to the central nervous system (CNS) in general, and the hypothalamic-pituitary-adrenal axis in particular, which has been proposed as a central biological pathway, through which diverse aetiological factors combine to produce the array of symptoms that are associated with the syndrome. Finally, the
literature on the treatment of CFS will be assessed with respect to how it informs the
debate about the factors that cause and maintain the syndrome.

Pathological Studies

*Infectious Illness and CFS*

The historical connections to unexplained epidemic outbreaks, and the fact that many
sufferers reported a viral-like onset, meant that research into the aetiology of CFS
originally focused on the search for a common infective agent. As has been described in
earlier sections, the resurgence of interest in the syndrome was triggered, in part, by a
report in the early 1980s that made a connection between the symptoms associated with
CFS and the Epstein-Barr virus (EBV: Tobi et al., 1982). These investigators examined
a group of patients with unexplained prolonged illness, characterised by low-grade fever,
myalgia, emotional distress, general malaise and weakness. They found significantly
elevated antibody responses to two EBV antigens, which would normally be expected to
occur only during the acute phase of EBV infection. The authors hypothesised that the
unexplained symptom complex resulted from reactivation of the virus, although they
also countenanced the possibility that abnormalities in immune regulation arising from
the original infection may be responsible (Tobi et al., 1982).
In 1985, two groups simultaneously published findings of the same nature. Their patient groups were more clearly CFS-like than those in the Tobi et al. (1982) study, in that disabling fatigue was primary among a cluster of symptoms including myalgia, nervous system symptoms, and depression. In 39 of 44 (Jones et al., 1985) and 20 of 31 (Straus et al., 1985) patients respectively, the same elevations in immune response to the same EBV antigens (the viral capsid antigen and the restricted component of the early EBV antigen) were found. Although the authors were cautious in their interpretation of the data and its implications, the use of EBV serologies as a diagnostic marker for the syndrome became widespread, as did the term ‘chronic Epstein-Barr virus infection’ (Merlin, 1986).

Within a relatively short period, a specific actiological role for EBV in CFS was almost completely discounted. In the same year as EBV-CFS links were being made, Horowitz, Henle, Henle, Rudnick and Latts (1985) showed that similar responses to the EBV antigens to those detected in the CFS-like groups were present in healthy individuals for as long as eight and a half years following the acute infectious episode. Merlin (1986) had cast doubt on the reliability of widespread laboratory testing as a diagnostic tool, and this was supported by a CDC study (Holmes et al., 1987) that demonstrated marked inter- and intra- laboratory variation in results. Soon after this, Buchwald et al. (1987), Hellinger et al. (1988) and Gold et al. (1990) demonstrated that the response to EBV antigens was unable to discriminate between cases of CFS and controls. Finally,
antiviral agents that should have controlled the virus had no effect on symptomatology (Straus, et al., 1988).

While the above evidence indicates that chronic EBV infection is almost certainly not responsible for most cases of CFS, a recent prospective study suggests that EBV and other viruses that can induce glandular fever may be a trigger for the disorder in some patients. White et al. (1998) monitored 250 primary care patients who presented with either glandular fever (GF) or upper respiratory tract infection (URTI) at primary care clinics. Three groups of patients were compared over time: those with GF related to EBV, those with GF due to a non-EBV infection and those with URTI. After six months, 10% of those who had EBV induced GF remained incapacitated to the extent that they met the CDC criteria for CFS (Fukuda et al., 1994). Similarly, 9% of the non-EBV GF qualified for the diagnosis of CFS. None of those patients who had been diagnosed with URTI met the CDC criteria for CFS at six months. In an earlier prospective study, Wessely et al. (1995) had found that URTIs or other minor, transient infections reported in primary care were not related to the development of CFS.

Taken together, these results suggest that, although URTIs are not associated with increased risk of developing CFS, EBV and other glandular fever producing viruses may have a role in the aetiology of a proportion of cases. An interesting question arises from these studies as to whether the infections that lead to glandular fever per se are related to the development of CFS in some instances, or whether it is factors that are associated with them, such as a long recovery period.
Other viruses from the Human Herpes Virus (HHV) family, such as HHV-6 and HHV-7, have been investigated in connection with CFS (Buchwald et al., 1992; Dale et al., 1989; Di Luca et al., 1995; Josephs et al., 1991). Buchwald et al. (1992) examined chronically fatigued patients following the Lake Tahoe outbreak, and found evidence of active HHV-6 replication in 70% of patients compared to only 20% of controls. The authors indicated that, while impressive, the results may have simply reflected a reactivation of the virus, which may have been secondary to immune dysfunction and, therefore, merely an epiphenomenon. A direct relationship between HHV-6 and CFS symptomatology could not be assumed on the basis of these results, which were also of uncertain generalisability, given that the study had centred around what appeared to be a specific, localised outbreak (Buchwald et al., 1992). Previous reports had also implicated HHV-6 in CFS (Dale et al., 1989; Josephs et al., 1991). A recent, well controlled study of EBV, HHV-6, HHV-7 and cytomegalovirus (CMV) in CFS patients and healthy controls found no differences in the detection of any of these viruses (Wallace, Natelson, Gause & Hay, 1999). At most, it is possible to say that the HHV-6 appears to be associated with CFS in some cases, and may have a role in initiating the disorder, similar to that hypothesised for EBV and some other infections.

Two other families of viruses have been studied extensively in CFS patients: enteroviruses and retroviruses. Enteroviruses, which include agents that produce poliomyelitis, have been a focus of study, particularly in the United Kingdom. This is primarily as a result of the previously discussed historical links between CFS and
epidemic myalgic encephalomyelitis. Enteroviruses also include the Coxackie and ECHO (Entero Cytopathogenic Human Orphan) viruses. Enterovirus infections are ubiquitous among the human population and are most commonly asymptomatic, although some can produce conditions of varying severity, from common colds and bronchitis to pneumonitis, meningitis and, poliomyelitis (Morello et al, 1984).

The evidence for enteroviral involvement in any more than a small minority of cases of CFS is weak. Some studies have reported evidence of persistent Coxsackie B infection in a higher proportion of CFS patients compared to healthy controls (Archard, Bowles, Bhan, Bell & Doyle, 1988; Yousef et al., 1988). Even so, this result reflected the presence of the virus in only a minority of CFS patients compared to a significantly smaller minority of controls. Miller et al. (1991) conducted a case-control study of Coxsackie B in 243 patients with post-viral fatigue syndrome and found almost identical antibody levels in CFS patients and controls. They concluded that the presence of Coxsackie B antibodies was of no diagnostic significance. Gow et al. (1991) originally found evidence of enteroviral RNA in muscle biopsies in 53% of CFS sufferers compared to only 15% of controls. A later, more comprehensive study was unable to replicate these findings (Gow et al., 1994).

Another study of 83 people with presumed viral meningitis, found higher rates of chronic fatigue and CFS than generally reported in primary care. However, these participants were no different to a control group of 78 patients who had suffered from
non-enteroviral and non-CNS related infections (Hotopf, Noah & Wessely, 1996).

Interestingly, this study did find that premorbid history of psychological disorder was a predictor of those who subsequently developed CFS. As in the case of EBV, this suggests that if enteroviruses are a risk factor for CFS, their effect is non-specific and is likely to be mediated by other factors.

Retroviruses are ribonucliec acid (RNA) viruses that contain the enzyme reverse transcriptase in the virion. Reverse transcriptase is so named because, in an inversion of the usual process, it enables the virus to use its RNA as a template to manufacture DNA. This viral DNA is then integrated into the DNA of the host cell, where it can replicate itself (Anderson, Anderson & Glanze, 1998). Retroviruses, such as the Human T cell lymphotropic viruses (HTLV-1 and HTLV-2) are associated with cancers such as leukemia and lymphoma, while another, the human immunodeficiency virus (HIV), is the agent responsible for acquired immunodeficiency syndrome (AIDS).

Retroviruses became a focus of intense attention in 1991 when De Freitas and colleagues reported evidence of the presence of HTLV-2-like sequences in a substantial majority of their sample of adults and children with CFS (De Freitas et al., 1991). Intriguingly, the sequences were also apparent in a proportion of healthy controls who had had sexual or casual contact with members of the patient group, but in none of another group of controls who had not been exposed to patients (De Freitas et al., 1991). The authors concluded that there was an association between the HTLV-2-like virus and CFS. While these findings caused a sensation at the time, they have not been replicated, nor have any
of a number of other retroviruses been able to be linked specifically with CFS (Gow et al., 1992; Heneine et al., 1994). While possibilities remain that a novel retrovirus, or variant of a known one, may have been missed (Heneine et al., 1994), the evidence collected to date offers no convincing evidence for retroviral involvement in CFS.

A number of other viral and non-viral agents have been examined in CFS (Fekety, 1994), including species of Borrelia (Coyte, Krupp, Doscher & Amin 1994) and, more recently, Mycoplasma (Vojdani et al., 1998). While it would appear that some viruses, such as EBV, are a risk factor for CFS, it is increasingly being accepted that a specific infective aetiology for CFS is unlikely to be demonstrated (Demitrack, 1996). Rather, infectious illness is viewed more as one of a number of physical and emotional stressors that seem to be able to trigger the condition.

**Immune Functioning in CFS**

As it became increasingly clear that none of the infectious agents suspected of producing CFS could, on their own, account for the illness in more than a minority of patients, research attention turned to the possibility that abnormal functioning of the immune system might be responsible. In part, the search for immune abnormalities was an indirect way for researchers to investigate the presence of infection (Strober, 1994). However, in theory, a dysfunctioning immune system could, on its own, directly
generate some of the principal symptoms of CFS; for example, alterations in levels of
certain cytokines are associated with symptoms such as fever, fatigue, myalgia and sleep
disturbance (Moldofsky, 1993). On the other hand, a weakened or disturbed immune
system might have a less direct aetiological role, by allowing the reactivation of latent
infections, or abnormally responding to infection in general.

The general complexity of the immune system, and the methods used to investigate it,
makes it difficult for most people outside the field to critically evaluate studies in this
area. This task is made even more complex in the study of CFS by the existence of a
large number of studies of many different immune parameters, often with divergent or
contradictory results. Inconsistencies are likely to be due largely to the use of
heterogeneous patient and control populations across studies and also to the
methodological complexity and sensitivity of the assay techniques used to measure
immune parameters (Demitrack, 1996; Strober, 1994). Strober (1994) also pointed out
that the immune alterations that have been identified have generally been subtle and,
while of statistical significance, their physiological and, more particularly, clinical
significance remains unclear.

In one of the earliest studies that looked specifically at immune function in CFS patients,
Lloyd, Wakefield, Boughton and Dwyer (1989) compared 100 CFS patients with 100
age- and sex-matched healthy controls on various measures of cellular and humoral
immunity. They reported significant overall reductions in T cell numbers, and in the
CD4 and CD8 subsets in particular. Both in vivo and in vitro measures indicated a significant reduction in T cell function. Overall, immunoglobulin (Ig) levels were normal, including IgG-subclass levels, which are involved in host responses to bacterial, fungal and viral infection. IgG1 and IgG3 subsets were found to be deficient in a minority of patients, with lower overall levels of IgG1 in the CFS group. Abnormalities of cellular and humoral immunity were not correlated, nor were they related to measures of disease severity. Later work by the same group also reported evidence of disturbed cellular immunity in the form of reduced CD4 and CD8 T cell numbers in CFS patients, this time compared to healthy controls and depressed patients (Lloyd, Hickie, Hickie, Dwyer & Wakefield, 1992). However, long-term follow up of 139 participants from two different treatment trials indicated that such abnormalities of cell-mediated immunity were not related to illness outcome (Wilson, Hickie, Lloyd, Hadzi-Pavlovic & Wakefield 1995).

**Cellular Immunity**

There have been many investigations of cellular immunity in CFS, with markedly variable findings. Some investigators have reported increases in CD8 T cells, with normal levels of the CD4 type (Klimas, Salvato, Morgan & Fletcher, 1990). In contrast, Gold et al. (1990) described normal CD8 numbers, but increased CD4 lymphocytes. Straus, Fritz, Dale, Gould and Strober (1993), on the other hand, reported reduced numbers of the CD4 subset. Landay, Jessop, Lonnete and Levy (1991) studied 147 CFS
patients and found no differences overall in CD4 and CD8 T cell subsets compared to either healthy controls or patients suffering from other illnesses, although data from the most severely ill of the CFS group suggested increased CD8 cell population and activation. A later, more detailed assessment of samples by the same group resulted in a report of reduced expression of CD11b and increased expression of CD38 and HLA-DR activation markers in the CFS group (Barker, Fujimura, Fadem, Landay & Levy, 1994). In contrast to this finding, Peakman, Deale, Field, Mahalingham and Wessely (1997) reported a decreased percentage of CD11b+ and CD8 cells.

With respect to natural killer (NK) cells, abnormal findings in CFS patients are common, although the nature of the abnormalities detected are as variable as that described for T cell populations. Some studies have reported decreases in NK cell number and/or activity (Barker et al., 1994; Gupta & Vayuregula, 1991; Masuda, Nozoc, Matsayama & Tanaka, 1994) while others have found increases (Gold et al., 1990; Peakman et al., 1997). Klimas et al. (1990) found increased numbers of NK cells, but a reduction in their activity. Along with a series of other immune parameters, Peakman et al. (1997) found that the increased NK cell count was not related to clinical outcome. In a review of the literature on immunological abnormalities in CFS, Strober (1994) suggested that many of the contradictions surrounding findings of NK cell number and function in CFS may be due to the fact that NK cells defined by the CD16 marker are generally reduced, while those defined by CD56+ are either increased, decreased, or normal. He pointed
out that NK-cells defined by CD56+ may, in fact be CD8+ T cells. Even with this
distinction, however, the evidence for NK cell alterations remains conflicting.

**Humoral Immunity**

As mentioned previously, Lloyd et al. (1989) reported that while overall Ig levels were
similar in CFS cases and healthy controls, specific deficiencies were apparent in the
IgG1 and IgG3 subclasses. Other laboratories had reported evidence of similar
deficiencies (Komaroff, Geiger & Wormsley, 1988; Linde, Hammarstrom & Smith,
1988; Read, Spickett, Harvey, Edwards & Larson, 1988). In keeping with previously
discussed immune parameters, evidence somewhat to the contrary is available, with a
more recent study finding significantly increased levels of the general IgG subclass in
just under 500 patients (Buchwald, Ashley, Pearlman, Kith, & Komaroff, 1996). This is
not directly contradictory, as an increase in IgG does not necessarily preclude a decrease
in some of its subsets. However, one of the same investigators has now reported finding
no differences in any of the IgG subclass levels between CFS patients and matched
healthy controls (Komaroff & Fagioli, 1996).

Strober (1994) expressed scepticism regarding the reliability and clinical significance of
the finding of Ig deficiencies. As mentioned earlier, Lloyd et al. (1989) had already
noted that immune parameters, including Ig levels, were not associated with symptom
severity. Several studies have trialed intravenous administration of gamma globulin,
with conflicting results. Peterson et al. (1990) reported no significant improvement in their cohort, while Lloyd et al. (1990), using a higher dose, reported significant improvement in 43% of patients. A more recent trial by this second group, however, failed to replicate their earlier findings, and concluded that Ig therapy for CFS could not be recommended (Vollmer-Conna et al., 1997).

More recently, attention has moved to the possible role of cytokines in CFS. Cytokines, such as interferons (IFN), interleukins (IL) and lymphokines, are proteins that facilitate cell to cell communication and coordination of T cell and antibody interactions. Cytokines amplify immune reactivity and the effectiveness of the immune response (Anderson et al., 1998). Overproduction or administration of some cytokines is known to produce symptoms associated with CFS, such as fever, fatigue, myalgia, sleep dysregulation and neuropsychiatric disturbances. Cytokines, therefore, have been a logical area of investigation (Lloyd, Hickie & Wakefield, 1994; Moldofsky, 1993).

Although circumstantial evidence is suggestive of cytokine involvement in CFS, clear and consistent cytokine anomalies are yet to be demonstrated in CFS patients. Significant increases in circulating level of some cytokine classes have been reported by a number of investigators (Chao et al., 1991; Cheney, Dorman & Bell, 1989; Patarca, Klimas, Lughtendorf, Antoni & Fletcher, 1994), although there is also contrary evidence (Lloyd, Hickie, Brockman, Dwyer & Wakefield, 1991; Linde et al., 1992; Mortc,
Castilla, Civiera, Serrano, & Prieto, 1989; Straus, Dale, Peter & Dinarello, 1989). Lloyd, Gandevia, Brockman, Hales & Wakefield (1994) compared cytokine response to prolonged exercise in CFS patients and a matched healthy control group. Following exercise, serum levels of IL-1 and IFN-α, which had been previously demonstrated to increase in response to vigorous exercise in healthy individuals, remained below assay detection limits in both groups. The isometric exercise employed in this study may not have been intense enough to produce a cytokine response (Lloyd et al., 1994). A paradoxical finding in this study was that, while fatigue and confusion scores increased in healthy controls, as expected in response to exercise, CFS values actually fell slightly.

Despite the lack of success in demonstrating a cytokine dysfunction in CFS, the hypothesis remains viable. Lloyd et al. (1994) suggested that cytokine abnormalities could still underlay some of the symptoms of CFS, but that they may only be apparent in very small amounts in cerebrospinal fluid or serum, or perhaps only within specific areas of the CNS. These researchers also point out some methodological issues, such as the use of single sampling protocols and different assay techniques, that have limited the comparability and conclusiveness of studies in the area. Strober (1994) also suggested that the cytokine hypothesis is unresolved, and that more sensitive assay techniques may lead to the discovery of abnormalities. He also noted that rapid clearance rates of cytokines such as IL-2 and IFN-γ may be responsible for in vitro abnormalities not being
reproduced in vivo. Finally, Strober (1994) noted that the set of known cytokines is incomplete, and that it may be undiscovered proteins that hold the key.

Despite the conflicting nature of much of the research in the area, many authors now agree that the bulk of evidence indicates that immune function is subtly altered in CFS patients. Apart from the continued drive to improve the consistency of findings regarding immune changes in CFS, research in the area also faces the challenge of demonstrating their clinical specificity and significance. Various immune changes, such as reductions in NK cell activity and alterations in cytokine function, are associated with depression and psychological stress (Irwin, 1991), sleep disturbances (Moldofsky, 1993) and levels of physical activity (Cannon et al., 1999). Given that all of these factors are associated with CFS to some degree, the question arises as to whether immune abnormalities detected in CFS patients are reflective of a primary disease process, or are secondary to other symptoms of the illness.

*Psychological Functioning in CFS*

To some degree, the study of psychological factors in CFS was as much a response to the lack of demonstrated infectious aetiology as was the study of immune function. As was the case with Neurasthenia, the lack of a clear organic pathology, and observations of high rates of psychiatric disturbance amongst CFS sufferers, led many clinicians and
researchers to speculate or conclude that the syndrome was better conceptualised as a psychiatric disturbance, such as depression or, perhaps, one of the somatoform disorders (Abbey & Garfinkel, 1991; Richmond, 1989). Without doubt, the question of whether CFS is best viewed as a psychiatric or medical illness has been the most controversial issue in both the scientific and broader communities.

As several investigators have pointed out, this debate is fuelled on both sides by the false but pervasive Cartesian view of physical and mental illness, and the social stigma associated with the latter (Demitrack & Abbey, 1996; Wessely et al., 1998). As such, much of the controversy is a social phenomenon, and has little relevance with respect to the central issues that motivate the investigation of CFS from a psychiatric perspective. Most significantly, it has been repeatedly demonstrated that psychiatric disorders, such as depressive, anxiety and somatoform disorders, affect between 50% and 80% of CFS sufferers (Fischler, Cluydt, De Gucht, Kaufman & De Meirleir, 1997; Hickie, Lloyd, Wakefield & Parker, 1990; Kruesi, Dale & Straus, 1989; Lane, Manu & Matthews, 1991; Wessely, Chalder, Hirsch, Wallace & Wright, 1997). Apart from identifying psychiatric illness as an important diagnostic and treatment issue in the majority of CFS sufferers, this, combined with the symptomatic overlap between CFS and a number of psychiatric illnesses, is suggestive of a degree of shared pathology or vulnerability.
Psychiatric Diagnoses in CFS Patients

Depression and Anxiety

Major depression is the most commonly diagnosed psychiatric condition in CFS sufferers. Generally, the proportion of CFS sufferers who have been assessed (via structured psychiatric interview) as having met the criteria for a major depressive episode at some stage during their illness has been estimated at between 35% and 55% (Hickie et al., 1990; Johnson, DeLuca & Natelson, 1996; Katon, Buchwald, Simon, Russo & Mcasc, 1991; Krucesi et al., 1989; Manu, Matthews & Lane, 1988; Taerk, Toner, Salit, Garfinkel & Ozcrsky, 1987). Although Hickie et al. (1990) reported pre-CFS rates of major depression to be no higher than general community prevalence figures (12.5%), a number of other groups have reported substantially higher rates, of up to 50% (Katon et al., 1991; Krucesi et al., 1989; Taerk et al., 1987). It is likely that differences in CFS case criteria, and in the methods used to determine the presence of psychiatric conditions were responsible for these differences, as well as the usual problems associated with retrospective diagnoses.

The prevalence of anxiety disorders in CFS patients has also been reported as increased compared to general population figures (Fischler et al., 1997; Hickie et al., 1996; Katon et al., 1991; Krucesi et al., 1989; Manu, Matthews & Lane, 1991; Taerk et al., 1987). A recent study has reported high rates of generalised anxiety disorder (GAD) in CFS
sufferers; 57% compared to only 14% in medical controls (Fischler et al., 1997). Although the authors noted that higher rates of GAD may have resulted partially from the interview technique, in which interviewers actively discouraged the minimisation of psychological symptoms, they also suggested that previous studies may have underestimated the prevalence of anxiety disorders in CFS due to the fact that earlier classification systems excluded other Axis 1 diagnoses when a mood disorder was present.

There is substantial diagnostic overlap between the DSM-IV criteria for major depression and CFS, and both are heterogeneous conditions with indistinct boundaries. Conceptualisations of CFS as misdiagnosed major depression, however, are undermined by a number of phenomenological differences between the disorders. CFS patients rarely express some of the cognitive features that are common in major depression, such as low self-esteem, guilt, suicidal ideation and hopelessness (Powell, Dolan & Wessely, 1990), nor do they often experience anhedonia, weight loss or demonstrate psychomotor slowing (Hickie, Lloyd & Wakefield, 1995). Differences in diurnal changes in mood (Stone et al., 1994), sleep structure abnormalities (Demitrack, 1996) and some aspects of neuroendocrine functioning (Demitrack, 1991) also indicate that CFS is qualitatively different to depression.

It is perhaps more reasonable to hypothesise that depression and/or anxiety is a common reaction to CFS. However, studies comparing CFS with other chronic, disabling
medical conditions such as neuromuscular disorders, rheumatoid arthritis and chronic muscle disease, show that the rates of psychiatric disorder are still substantially higher in CFS patients (Katon et al., 1991; Wessely & Powell, 1989; Wood, Bentall, Gopfert & Edwards, 1991). Of course, CFS is different to these disorders in important ways that might contribute to the genesis of affective and anxiety disorders in particular. The CFS patient suffers from a disabling illness that is inexplicable, unpredictable, uncontrollable, invisible to most others, and regularly socially invalidated (English, 1991). This scenario fits well into major cognitive models of the aetiology of depression (e.g. Abramson, Seligman & Teasedale, 1978) and anxiety (Barlow, 1988). Even so, whether these differences between CFS and other illnesses are enough to account for the sometime manifold increase in relative rates of psychiatric disorder is unknown. Further, the notion that depression and anxiety are purely responses to CFS is undermined by the number of reports of higher premorbid rates of psychiatric diagnoses in CFS patients (Wessely et al., 1998).

It is possible that depression and anxiety are prominent in CFS sufferers because there is a degree of shared pathology between the three disorders. The mechanisms that increase vulnerability to depression might also operate in CFS. On the other hand, physiological changes that occur as a result of either disorder might themselves increase an individual's vulnerability to the other. Even though the disorders can be separated on phenomenological grounds, a degree of shared pathology between CFS and depression is suggested by their symptomatological overlap, epidemiological similarity, and the fact
that many of the physiological abnormalities of immunity and brain function that are noted in CFS are also found in depressed patients.

Somatisation Disorder

Although it is relatively less common than major depression and anxiety disorders, somatisation disorder (SD) is probably the most controversial of all psychiatric diagnoses made in CFS patients. From the patient’s point of view, this is understandable, given that the basis of the diagnosis of SD is the presence of medical symptoms without apparent physical cause, and sufferers are usually seen as providing exaggerated, inconsistent accounts of their symptoms and medical histories (American Psychiatric Association, 1994). Theorics of the actiology of somatoform disorders commonly hold that the conscious or unconscious production of symptoms is reinforced by some form of secondary gain, such as attention from family or friends (Davison & Neale, 1998; Sackheim, Nordlie & Gur, 1979). Nevertheless, the criteria for SD are similar to those for CFS, the main difference being that physical complaints have to have been apparent before the age of 30 years. Also, like CFS, SD is more common amongst women (Viederman, 1986) and has high comorbidity with anxiety and depressive disorders (Golding, Smith & Kasher, 1991).

SD has most commonly been reported in groups of CFS sufferers at rates of between 10% and 20% (Fischler et al., 1997; Katon et al., 1991; Manu et al., 1988; Wessely &
Powell, 1989). One study found no cases of SD among their patients (Hickie et al., 1990), another only 7% (Kruesi et al., 1989), while Lane, Manu and Matthews (1991) reported a figure of 28%. Although these rates are substantially higher than those of 0.2% to 2% reported for SD in the general population (American Psychiatric Association, 1994), they compare with the rates found in general medical patients of 8%, rising to 14% in patients with uncertain diagnoses (Van Hemert, Hengeveld, Bolk, Rooijmans & Vandenbroucke, 1993).

The CDC’s attempt, via their original case definition (Holmes et al., 1988), to define a homogenous patient group by requiring the presence of at least eight symptom criteria, in addition to fatigue, inadvertently led to a higher proportion of patients with SD and other psychiatric diagnoses being labelled as CFS (Katon & Russo, 1992). The decision by the 1994 committee (Fukuda et al., 1994) not to exclude SD patients from the diagnosis of CFS has been questioned on the basis of the substantial difficulties of diagnosing the disorder in this group (Abbey, 1996). Hickie et al. (1995) have shown that just over a quarter of patients labelled as CFS can be statistically differentiated on the basis of features such as illness duration, severity of current psychological morbidity, spontaneous recovery, utilisation of medical services and CD8 T cell subset counts. They argue that this group should be classified within the SDs rather than CFS, as this would reduce the clinical heterogeneity of patients and facilitate research in the area.
Psychological Characteristics and Functioning in CFS

Non-psychiatric aspects of psychological functioning in CFS patients, such as: personality, self-efficacy, and illness attribution and coping styles have also been investigated. A number of retrospective studies have reported that CFS sufferers tend to describe premorbid lifestyles that are characterised by particularly hard driving work, physical and social lives (Lewis, Cooper & Bennett, 1994; Van Houdenhove, Onghena, Neeriks & Hellin, 1995; Warc, 1993), which are underpinned by the need to meet high personal performance standards (Ware, 1993). While much has been made of such findings in the popular literature on CFS, no prospective studies have been conducted in order to determine whether these characterisations provide a true reflection of the general premorbid functioning of people with CFS, or whether they are the product of recall bias.

A group of 30 non-depressed CFS patients were found to score lower on a measure of neuroticism than a group of major depression patients, but higher than healthy controls (Buckley et al., 1999). CFS patients also scored lower than controls on an extroversion scale. The authors suggested that these findings are more likely to be due to patients' reactions to chronic illness, rather than reflective of intrinsic personality traits. Schmaling and Jones (1996) found that their groups of 53 CFS patients scored significantly higher on the neurotic triad (scales 1, 2 and 3) of the Minnesota Multiphasic Personality Inventory (MMPI) than a group of 43 healthy controls, although, again, this
was likely to be a reaction to the illness, given that many of the items that load on these scales overlap and relate to somatic concerns and cognitive malfunctioning.

Patients' beliefs and behaviour relating to CFS have been associated with outcome and disability. Both cross-sectional and prospective studies have reported that patients who more strongly attribute their symptoms to physical rather than psychological or social causes tend to have more severe symptoms and poorer outcome (Chalder, Power & Wessley, 1996; Vercoulen et al., 1996; Wilson et al., 1994). A recent study of the association between illness beliefs and treatment outcome failed to find such a relationship, although beliefs about the negative consequences of exercise and subsequent avoidance of activity were related to poor treatment outcome (Deale, Chalder & Wessely, 1998). Other investigators have also indicated that accommodating to the illness and avoidance of activity was associated with greater functional impairment (Ray, Jefferies & Weir, 1995 & 1997).

It seems reasonable to suggest that physical attributions may lead to a reduction in patients' sense of being able to control or predict their symptoms, which, in turn, may lead to behavioural disengagement and avoidance of activities that are perceived to have the potential to exacerbate symptoms. This may be an adaptive response to fatigue in the early stages of the illness. However, over time, the consequences of the consistent and wholesale application of such a strategy, such as physical deconditioning and social withdrawal, may make it counter-productive (Ray et al., 1995; Wessely, David, Butler &
Chalder, 1990). Even though much of the data upon which such conceptualisations are based has been collected using longitudinal designs, the causal relationship between attributions, beliefs, behaviour and outcome is still unclear. It may be that patients’ perceptions and coping styles are affected to some degree by the nature of their illness, with those with more severe or entrenched disease processes being more likely to make physical attributions or adopt avoidance as a way of dealing with their CFS (Wilson et al., 1994). It is also uncertain as to whether attributions and coping styles have any real impact upon CFS per se, or whether they are simply associated with health status in general. A degree of functional impairment due to physical deconditioning is a natural consequence of the avoidance of activity whether one has an underlying illness or not. Thus, while it can hardly be doubted that such functional impairment due to inactivity contributes to the impact of the illness on the lives of its sufferers, it is not clear whether or how attitudes and behaviour impact upon the fundamental dysfunction(s) that may underlie CFS.

**Interactions Between Infection, Psychological Functioning and Stress**

A number of studies have demonstrated a relationship between prolonged recovery from viral illness and premorbid personality or psychiatric disorder. As outlined in Chapter 1, psychological factors were implicated in prolonged recovery from brucella infection during the 1950s by Spink (1951) and then Imboden et al. (1959). Also discussed in
Chapter 1, was the prospective study by Imboden et al. (1961) in which it was demonstrated that depression scores, assessed months prior to infection by the influenza virus, were predictive of prolonged recovery. These results were impressive, although 'prolonged' in this case was a period of only 3-6 weeks, as opposed to the minimum of 6 months required to qualify for the CFS diagnosis.

More recent studies have also indicated an association between premorbid psychological functioning and prolonged recovery from infection. Wessely et al. (1995) prospectively surveyed all patients in several general medical practices for fatigue and psychological morbidity. For 6 months, the investigators followed a cohort of 1199 patients aged between 18 and 45 years who subsequently presented to one of the practices with suspected infection, and a similar number of controls, who presented for reasons other than infection. At 6 months, patients from both groups who reported significant fatigue underwent a thorough assessment to establish whether they met the criteria for the various case definitions of CFS. A group of age- and sex-matched controls, selected from those who had not reported significant fatigue, were also assessed.

Similar proportions of patients from the infection and non-infection groups reported chronic fatigue after 6 months, and there was no difference in the proportions who met the case criteria for CFS. Infection, therefore, did not predict the subsequent development of either chronic fatigue or CFS. In contrast, increased fatigue and psychiatric morbidity assessed prior to original presentation were both found to predict
prolonged fatigue and CFS (Wessely et al., 1995). As has been noted earlier, these results do not discount the possible roles of more severe prolonged infectious illnesses in the development of CFS. However, they do suggest that premorbid fatigue and psychological distress are risk factors for CF and CFS. As has already been outlined, another study by the same group (Hotopf et al., 1996) found that a history of psychiatric disorder was a predictor of the development of CFS in a group of viral meningitis sufferers and others suffering from non-enteroviral, non-CNS infections.

While these results provide evidence suggestive of a psychological basis for CFS, evidence from other research indicates that the relationship between psychological factors, infections and prolonged fatigue is not straightforward. Demitrack and Abbey (1996) reviewed two studies that indicated that psychological factors could predispose individuals to infection. Kasl, Evans and Niederman (1979) studied psychosocial factors and the development and expression of EBV-related glandular fever in an entire cohort of first year students enrolled at the West Point Military Academy in the USA. The investigators reported that factors reflecting greater academic pressure, such as higher motivation for academic achievement, having a father described as an ‘overachiever’ and poorer academic performance, predicted not only the development of glandular fever, but also EBV seroconversion in students who remained asymptomatic.

Cohen, Tyrell and Smith (1991) conducted an experimental examination of the relationship between psychological factors in 394 healthy subjects who were
deliberately exposed to one of five common cold infections or to placebo. Prior to exposure, participants were assessed with respect to their psychological and psychosocial functioning and factors such as negative affect, stressful life events and coping were used to calculate a ‘stress index’. Higher levels of psychological stress prior to exposure were associated with higher rates of infection, indicating that increased psychological stress was related to reduced host resistance.

The interaction between infection and psychological factors is complicated further by findings that infection can precipitate psychological disorders, namely depression and anxiety, in some patients. Increases in the rates of mood and anxiety disorders following glandular fever in particular, have been reported (Cadie, Nye & Storey, 1976; White et al., 1998). White et al. (1998) found that prevalence rates for all psychiatric disorders almost doubled with the onset of infectious illness. New diagnoses of Major Depression were made at the onset of EBV related glandular fever in 28% of cases, compared to 14% of patients with non-EBV glandular fever and 11% of those with common URTIs. The prevalence of anxiety disorders also rose significantly following the onset of infectious illness, from 1% to 6%, but was not related to any specific infection. The median duration of depressive illness was only three weeks and, by six months, no psychiatric disorders were more prevalent than they were prior to infection.

More research into the interaction between psychological factors, infection and prolonged fatigue is needed. Although premorbid psychological functioning has been
linked to prolonged recovery from infectious illness, other evidence suggests that purely psychosomatic conceptualisations of CFS are simplistic and premature. In particular, evidence that psychological stress reduces host resistance to infection, and that psychological disorder is a reasonably common consequence of some infectious processes, strongly suggests that the interaction between psychological functioning and infection is complex and multidirectional. These issues highlight the inadequacy of the Cartesian view of psychological and physical illnesses.

The Association Between Stress, Personality, and the Onset and Maintenance of CFS

Anecdotal and empirical reports have identified stressful life events or circumstances as important aetiological and maintaining factors in CFS, irrespective of the occurrence of infection. Ray et al. (1998) interviewed 60 CFS sufferers regarding circumstances surrounding the onset of their illness. While 93% reported episodic or persistent infection in the period leading up to the onset of their illness, 82% also reported having an overactive lifestyle, and 77% said that they had experienced emotional strain associated with work, relationships and life events. Salit (1997) examined precipitating factors in 134 CFS patients and found that, although 72% of their sample reported an apparent infectious onset, definite or probable infection could be established in only 22% of these patients. Stressful life events, on the other hand, were reported to have occurred in the year prior to CFS onset in 85% of patients, compared to only 6% of a
healthy control group. Theorell, Blomkvist, Lindh and Evengard (1999) also reported increased rates of infection and negative life events in 46 CFS patients immediately prior to illness onset. The CFS group was compared to healthy controls, who were asked to recall events in the year prior to a ‘very difficult period’ in their lives. A smaller retrospective case-control study found that 95% of a CFS group reported significant stressful events in the five years prior to their illness, compared to 55% of healthy controls (Dobbins, Natelson, Brassloff, Drastal & Sisto, 1995). In contrast to these findings, Lewis, Cooper and Bennett (1994) found no differences in either the number or severity of stressful life events in their group of 47 CFS sufferers, compared with irritable bowel patents and healthy controls. All of these studies rely on retrospective accounts, a methodology that is open to recall errors and bias. In a prospective study of stressful life events and prolonged recovery from infection, Bruce-Jones, White, Thomas and Clare (1994) found that social adversity was associated with occurrence of psychiatric disorder (mainly depression) following infectious illness, but not with the onset of a pure fatigue syndrome or delayed physical recovery alone.

Ray and Jefferies (1995) studied the effects of stress in the course of CFS and found that stressful life events were significantly, although weakly, associated with increases in anxiety levels in CFS sufferers, but not with measures of fatigue, impairment or depression. Conversely, positive events and outcomes were significantly associated with improvements on all measures. Another study reported that the stress related to the occurrence of Hurricane Andrew resulted in a significant exacerbation of symptoms of
49 CFS patients residing in storm affected areas (Lutgendorf et al., 1995). Patients who lived where the storm impacted most directly experienced a greater deterioration in their health status than those in less affected areas. Finally, Wood, Bentall, Gopfert, Dewey and Edwards (1994) studied the psychological and physiological consequences of a mildly distressing cognitive task in CFS, psychiatric and muscular dystrophy patients. They found that the CFS group experienced a greater increase in both physical and psychological symptoms following the task than either of the two control groups.

A long-established problem with the use of the number of negative life events as an indicator of the amount of stress to which an individual has been exposed, is that the level of stress experienced as a result of any particular event, or stressor, is mediated by factors within the individual and their environment. Individual differences in perceptions of both the significance of the stressor and the individual's ability to deal with it, (Lazarus, 1966) coping styles (Lazarus & Folkman, 1984) and the quantity and quality of social support available (Cohen & Wills, 1985), have all been identified as having a significant influence on the extent to which negative events are experienced as stressful. Therefore, if CFS sufferers, as a group, systematically differed from comparison groups on any of these variables, their exposure to stress may differ, even when the number and severity of life events do not.

In this context, it is interesting to note that although Lewis et al. (1994) found no increase in the number or severity of life events in CFS sufferers compared to irritable
bowel syndrome patients and healthy controls, the CFS group reported more problem-focused coping strategies and poorer social support than either of the comparison groups. The authors suggested that, while problem focused strategies such as confrontive coping, planful problem solving and seeking social support, can be effective in reducing stress, this may only be in situations in which an individual has some degree of control over outcomes. The authors also speculated that the consistent application of strategies that require the individual to dwell on problems they cannot solve may be inappropriate and counter-productive, in that it can lead to sustained arousal, distress and the negative physiological sequelae associated with these emotional states.

These findings, along with those previously described with respect to personality and premorbid psychiatric history, raise the possibility that physical (ie genetic) and psychosocial (personality, social environment) factors may predispose some individuals to CFS, at least in part by altering their psychological, behavioural and physiological responses to stressors.

*The Central Nervous System and CFS*

The central nervous system (CNS) is a logical focus for research into CFS for several reasons. Firstly, the number and diversity of the symptoms associated with the syndrome are suggestive of a central dysfunction. Second, the variously reported
cognitive deficits, neuropsychiatric disturbances and sleep dysregulation implicate the CNS in the disease process. Finally, disturbance to neuroendocrine functioning in particular has considerable theoretical appeal with respect to its ability to account for much of the phenomenology associated with CFS.

**General Structure and Functioning**

Various imaging techniques are available to assist in the investigation of neuroanatomic correlates of various disease processes. Magnetic resonance imaging (MRI) and computer tomography (CT) are methods which map the structural integrity of the living brain, while the advanced scanning technologies of positron emission tomography (PET) and single-positron emission computer tomography (SPECT) detect functional changes. PET and SPECT use advanced computer image construction techniques to illustrate regional cerebral function, metabolism and chemistry. Recently, these methods have been applied in the search for structural and/or functional alterations in the central nervous systems of CFS patients.

Buchwald et al. (1992) reported MRI abnormalities in 78% of 144 patients from the Lake Tahoe epidemic. The abnormalities were in the form of high signal intensity foci, generally located within the subcortical white matter. Abnormal scans were, however, also reported in 21% of control participants and, in patients who were followed up, the abnormalities persisted in spite of symptom resolution. It is unclear how generalisable
these findings are with respect to CFS, given that the patients in this study were part of a specific geographical cohort associated with an epidemic, and demonstrated a range of symptoms, such as seizures and ataxia, that are not usually associated with CFS. Some methodological issues, like the lack of blinded assessment of scans, also limit the reliability of these findings.

Two other studies using MRI scanning to assess the structural integrity of the brains of CFS patients have found similar abnormalities, although in substantially smaller proportions of participants than that reported by Buchwald et al. (1992). Natelson, Cohen, Brassloff and Lcc (1994) reported abnormalities in 14 of 52 CFS patients studied. As with the Buchwald et al. (1992) study, the most common types of abnormality were foci of high intensity signal in cerebral white matter, although some patients demonstrated ventricular or sulcal enlargement. In contrast, abnormalities were present in only 1 of 52 control scans. In a group of 16 CFS patients, Schwartz et al. (1994) reported abnormalities in a non-significantly greater proportion of patients (50%) relative to controls (20%). These three studies suggest that structural brain abnormalities may be more common in patients with CFS than they are in healthy individuals. However, as is the case with many of the physiological changes that have been associated with the disorder, the clinical significance and specificity of these abnormalities is uncertain (Buchwald et al., 1992).
A number of studies of CFS patients have now reported altered blood flow in various brain regions. Most commonly, investigators have reported evidence of reduced blood flow in frontal (Goldstein, Mena, Juoanne & Lesser, 1995; Ichise et al., 1992; Troughton, Blacker & Vivan 1992) and temporal (Goldstein et al., 1995; Ichise et al., 1992) regions, while another group noted asymmetries in blood perfusion in the right and left temporal lobes (Simon, Cowden, Seastrunk, Weiner & Hickey, 1991). Costa, Tannock and Brostoff (1995) reported reduced blood perfusion throughout the brains of CFS patients, but noted hypoperfusion was particularly evident in the brainstem. A recent study found brain hypoperfusion in 13 of 18 CFS sufferers, although the brain regions involved varied between patients (Abu-Judeh et al., 1998).

The studies of brain structure and function in CFS using sophisticated scanning equipment generally suffer from the methodological difficulties that apply to other areas of CFS research, the main one being differences in screening methods leading to patient populations that are heterogeneous between, and often within, studies. Further, the heterogeneity of patient groups and methodological differences between studies is probably largely responsible for the inconsistency of findings between studies. Although it can be said that the neuroimaging studies of CFS patients are generally indicative of altered CNS structure and functioning, more controlled studies are required to elucidate the nature of abnormalities. The specificity of findings is also a major issue. In many of the studies cited here, although CFS patients differed from healthy control participants, their abnormalities were generally similar to those found in depressed
patients (Ichise et al., 1992; Goldstein et al., 1995; Schwartz et al. 1994b; Simon et al., 1991).

**Polysomnography**

Sleep disturbance is one of the most commonly reported problems in CFS. CFS patients report light, disturbed and unrefreshing nocturnal sleep (Krupp, Jandorf, Coyle & Mendelson, 1993) and excessive daytime sleepiness and sleep behaviour (Buchwald, Pascualy, Bombardier & Kith, 1994). Sharples Clements, Hawton & Sharpe (1997) found that 95% of CFS patients in their study complained of difficulty with their sleep of one kind or another.

Indeed, several studies point to high rates of diagnosable sleep disorders such as sleep apnoea (Buchwald et al., 1994; Krupp et al., 1993) and periodic limb movement disorder (Manu et al., 1994) in patients diagnosed with CFS. However, as Wessely et al. (1998) pointed out, these findings probably point to problems with differential diagnosis between CFS and sleep disorders, given that the presence of sleep disorders such as sleep apnoea and narcolepsy are part of the exclusionary criteria for CFS. The generalisability of the findings of some of these studies is also questionable, given that participants were selected on the basis of self reported sleep problems (Buchwald et al., 1994; Krupp et al., 1993).
Polysomnographic studies of the sleep of CFS patients have reported some abnormalities of sleep architecture, although the nature of disturbances found has varied. Moldofsky, Scrisbrick, England and Smythe (1975) conducted a polysomnographic study of patients suffering from Fibromyalgia (FM), known then as ‘Fibrositis’, and reported the occurrence of alpha-wave intrusions into non-REM sleep. This abnormality was found to be related to patients’ reports of unrefreshing sleep and overnight increases in muscle tenderness. The authors’ interpretation that their findings indicated an arousal disorder within sleep were supported by further work that showed that the abnormality could be induced in healthy, sedentary people by noise disruption of stage 4 sleep (Moldofsky & Scarisbrick, 1976). Even more significantly, a connection between this sleep anomaly and the symptoms of Fibromyalgia was suggested by the fact that healthy subjects in whom the alpha intrusions had been induced subsequently reported experiencing generalised aching and fatigue (Moldofsky & Scarisbrick, 1976). Other reports have also noted the presence of alpha intrusion into non-REM sleep in FM (Branco, Atalaia & Pavia, 1994; Simms, Gunderman, Howard & Goldenberg, 1988).

Given the symptomatological similarity between CFS and FM, it is not surprising that Moldofsky (1993) has suggested that the sleep abnormalities and ‘non-restorative sleep’ syndrome that has been linked to FM might also be present in CFS. While an early study did find evidence of alpha intrusion into non-REM sleep in 14 CFS patients (Whelton, Salit & Moldofsky, 1992), there has been no further demonstration of a clear
association. Manu et al. (1994) found that alpha intrusions were apparent in 8 of 30 consecutively referred patients with chronic fatigue and suggested that, although not associated specifically with CFS, this abnormality was a possible contributor to the illness in some non-depressed patients. Other studies have found that the main sleep abnormalities in CFS patients are reductions in sleep efficiency and more frequent awakenings (Krupp et al., 1993; Morriss et al., 1993; Stores, Fry & Crawford, 1997). In a study of 20 carefully selected CFS patients, screened to exclude depressive, anxiety and sleep disorders, Sharpely et al. (1997) found that CFS patients spent longer in bed, slept less efficiently, and spent more time awake after original sleep onset. Only seven individuals had abnormal polysomnographs, which entailed problems initiating and/or maintaining sleep.

These authors concluded that sleep abnormalities were unlikely to be a significant causal factor with respect to CFS symptomatology. It is also unclear as to whether sleep problems that are associated with the disorder are related to an underlying pathological process, or are secondary to behavioural factors associated with CFS, such as poor sleep hygiene and physical inactivity. It is reasonable, however, to conclude that disturbances to sleep are likely to contribute, at least as a maintaining factor, in an illness where fatigue is a primary symptom.
Neuroendocrine Function in CFS

The hypothalamic-pituitary-adrenal (HPA) axis is considered to be a pivotal agent in the coordinated physiological response to both physical and psychological stress (Sapolsky, 1992). In response to stressful stimuli, the hormone corticotrophin-releasing hormone (CRH), the principal activating hormone, and arginine vasopressin (AVP), an adjunctive secretagogue, are released from the paraventricular nucleus of the hypothalamus. These hormones stimulate receptors on the anterior pituitary, causing it to release adrenocorticotropic hormone (ACTH). In turn, ACTH stimulates the release of corticosteroids by the adrenals, the most significant of which, in humans, is cortisol (Sapolsky, 1992). Whether an individual is stressed or not, corticosteroids play an important role in homeostasis, and exert important effects on the metabolism of carbohydrate, proteins, fats and purines, as well as the regulation of electrolyte and water balance (Bowman & Rand, 1984). They are also central to the proper functioning of various tissues and organ systems, such as lymphoid and muscle tissue, and the renal, cardiovascular and nervous systems (Anderson et al., 1998).

The HPA axis has become a focus of interest in CFS research over the past decade. Primarily, this is because disturbances to the functioning of this system could, theoretically account for much of the symptomatology and other phenomena associated with the disorder (Demitrack et al., 1991). For example, corticosteroids have
an important influence on the proper functioning of the immune system, and exert inhibitory effects on the immune and anti-inflammatory responses (Anderson et al., 1998). Disturbances to electrolyte balance, carbohydrate metabolism and circulation that result from abnormally high or low circulating corticosteroid levels, produce muscle weakness and rapid fatiguability (Bowman & Rand, 1984). Alterations in corticosteroid levels are also associated with disturbances of mood and sleep (Anderson et al., 1998; Bowman & Rand, 1984).

Poteliakoff (1981) compared plasma cortisol levels in 25 chronically fatigued and 22 acutely fatigued patients with that of age- and sex-matched healthy controls. Reductions in plasma cortisol were noted in both fatigue groups, in conjunction with altered circadian patterns of capillary resistance and eosinophil counts. A decade later, Demitrack et al. (1991) published a comprehensive evaluation of HPA axis functioning in 30 patients meeting the 1988 CDC definition of CFS (Holmes et al., 1988), and in 72 healthy controls. These investigators found that CFS patients demonstrated reduced total 24-hour urine free cortisol excretion and reduced basal evening plasma total and free cortisol levels. In addition, CFS patients demonstrated increased evening ACTH levels, attenuated adrenal response to maximal ACTH stimulation, and blunted ACTH response to CRH administration. Interestingly, ACTH levels were positively correlated with measures of fatigue and depression.
The authors proposed that the combination of findings suggested that the mild hypocortisolism demonstrated in their CFS group was due to a deficiency in the release of CRH and/or other secretagogues (such as AVP). The origin of the proposed CRH deficiency remained unknown although, by deduction, it must have occurred either at or above the level of the hypothalamus. (Demitrack et al., 1991). Given that corticosteroid deficiencies have been shown to produce many of the symptoms associated with CFS, and the well-reported association between the onset of the syndrome and physical and emotional stress, the authors also suggested that a dysfunctional HPA axis may be the final common physiological pathway through which multiple and diverse aetiological factors combine to produce the symptom complex.

The potential implications of these findings were very encouraging. Reduced glucocorticoid secretion could, theoretically, account for much of the symptomatology of the disorder, as well as the associated phenomena, such as the various indices of mild immune activation that have been reported (Demitrack, 1997). Demitrack (1997) also pointed out that, apart from acting as the principal stimulus to the HPA axis, CRH has been shown to be a behaviourally active neurohormone which, when administered centrally to animals, induces signs of physical and behavioural arousal. He suggested, therefore, that a relative deficiency in the hormone could contribute both directly and indirectly (ie. by producing a corticosteroid deficiency).
Another interesting implication of these findings is the fact that these results seemed to physiologically differentiate CFS sufferers from patients with melancholic depression, in whom cortisol levels are usually increased (Carroll, Curtis & Mendels, 1976). Other neuroendocrine studies offered support for this distinction. In the year following the publication of the Demitrack et al. (1991) study, Bakheit, Behan, Dinan, Gray and Okeane (1992) reported that both male and female CFS patients demonstrated significantly greater prolactin responses to challenge with the selective serotonin_{1A} (5HT_{1A}) receptor agonist, buspirone, compared to depressed patients and healthy controls. The authors suggested that their findings indicated that serotonin (5HT) receptors were upregulated in patients with post-viral fatigue, but not in depressed patients. Although buspirone is known to also have some dopaminergic effects and is, therefore, not completely selective for 5HT receptors, these findings still indicated altered hypothalamic-pituitary function in CFS patients that differed qualitatively from that of people suffering from major depression.

The findings of Bearn et al. (1995) also offered limited support for serotoninergically mediated impairment of hypothalamic-pituitary responses to stress in CFS, with a blunted prolactin response to insulin-induced hypoglycaemia in non-depressed CFS patients compared to healthy controls. While growth hormone levels were non-significantly lower in the CFS group, no differences were observed in the responses of either ACTH or cortisol relative to the control group. In a second study, these investigators employed a neuroendocrine challenge paradigm with their patients using
the serotonergic agent d-fenfluramine. In contrast to the findings of Bakheit et al. (1992), CFS patients did not show an elevated prolactin response. This finding, however, is questionable, as control and CFS groups were not sex-matched. On the other hand, several investigators have repeated the findings of Bakheit et al. (1992) in CFS patients using buspirone (Sharpe et al., 1996) and d-fenfluramine (Cleare et al., 1995; Sharpe et al., 1996). One other study (Yatham et al., 1995) that failed to find altered prolactin responses to dl-fenfluramine, has been criticised on the basis that dl-fenfluramine is a less specific serotonergic agent than d-fenfluramine, and that their patient group was heterogeneous with respect to psychiatric history.

Results of the carefully controlled study by Cleare et al. (1995) offered strong support for both the altered serotonergically mediated hypothalamic-pituitary function reported in CFS sufferers by Bakheit et al. (1992) and the hypocortisolism reported by Demitrack et al. (1991). These investigators compared HPA axis and central 5HT functioning in 10 CFS patients who had been screened to exclude depression, 15 patients with major depression, and 25 healthy controls matched for sex, age, weight and menstrual cycle. Patients in the depressed group demonstrated the typical increases in circulating cortisol levels and blunted prolactin responses to d-fenfluramine administration compared to healthy controls. Conversely, the CFS group demonstrated significantly reduced cortisol levels and increased prolactin secretion in response to d-fenfluramine administration. These findings supported the contention that CFS and major depression are physiologically distinct entities, and that CFS is associated with hypocortisolism.
Although Scott and Dinan (1998) also reported reduced urinary free cortisol levels in CFS and high levels in depressed patients compared with healthy controls, some studies have failed to find clear evidence of hypocortisolism in CFS. Wood, Wessely, Papadopoulos, Poon and Checkley (1998) measured salivary cortisol levels in 10 non-depressed CFS participants and 10 healthy controls. Mean cortisol levels over the entire sampling period were actually slightly, though non-significantly, greater in the CFS group. Another group monitored 24-hour cortisol secretion patterns in CFS and control participants, and found no difference in either salivary or urinary cortisol levels (Young et al., 1998). McHale et al. (1998) measured morning and evening cortisol and ACTH levels in CFS patients and healthy controls. While they also found no evidence of an overall reduction of cortisol in the CFS group, they did find that the difference between morning and evening values was smaller in those patients, and that difference scores were positively correlated with measures of functional improvement and social functioning.

The reason for such inconsistency is likely to be, in part at least, due to methodological differences but also to the fact that cortisol levels are not particularly robust, and are subject to significant change by, among other factors, stressors and food intake. Evidence of HPA axis dysfunction in CFS arising from the various challenge studies is considerably more consistent. A series of recent papers from one laboratory in particular have variously reported that CFS patients demonstrate: blunted ACTH and
cortisol responses to CRH administration in a group of patients screened to exclude depression (Scott, Medbank & Dinan, 1998a); reduced cortisol response to low dose ACTH administration (Scott, Medbank & Dinan, 1998b); blunted ACTH responses to opiate antagonist administration, suggesting excessive opioid suppression was not the basis of HPA axis dysregulation (Scott, Burnett, Medbank & Dinan, 1998), and; blunted ACTH responses to CRH administration, with the normalisation of responses when CRH was administered in combination with the arginine vasopressin analogue, desmopressin (Scott, Medbank & Dinan, 1999). This last finding was suggested to indicate a possible increase in the vasopressinergic sensitivity of the anterior pituitary in CFS (Scott et al., 1999). Recently, this group has also published evidence of adrenal atrophy in CFS patients, using computer tomography to show that the right and left adrenals of eight CFS patients were 50% smaller than those measured in scans of 55 healthy individuals (Scott, Teh, Reznek, Martin, Sohaib & Dinan, 1999). The generalisability of these findings is yet to be determined, as CFS patients for this study were specifically selected on the basis of a subnormal response to ACTH administration.

Although the role of the HPA axis in CFS is by no means clear, the evidence collected so far generally supports the original conclusions of Demitrack et al. (1991), that a disturbance is present and that it is one which is qualitatively different to that normally associated with major depression. As has been discussed, Demitrack’s suggestion that HPA axis dysfunction is the final common biological pathway through which multiple aetiologies converge to produce CFS, has strong explanatory power with respect to
much of the phenomenology of CFS. This includes the apparent role of physical and emotional stress in its development and course; the major symptoms of fatigue and muscle weakness, and common findings in CFS patients of disturbances to immunity, sleep and mood. The validity of these theoretical connections is yet to be demonstrated empirically.

While research so far suggests that the nature of the disturbance appears to involve serotonergic neurons, its aetiology is unclear, as is the role of other neuroendocrine agents, such as vasopressin. What is also unclear is whether this disturbance, even if its presence and influence in CFS were to be established beyond doubt, actually represents a final common biological pathway for the development of CFS, or whether it is a subordinate dysfunction to an even more central disturbance. A possible candidate for such a role is the circadian system, which, as will be outlined in Chapter 4, plays a central role in the regulation of the HPA axis, as it does in all other hypothalamic-pituitary axes (Van Cauter, 1990).

**Intervention Studies**

Although treatment studies are undoubtedly motivated to some degree by the need to investigate means of increasing the options available to patients, they serve the important purpose of providing a 'top-down' approach to the exploration of the factors
that cause and maintain illness. This approach is based on the logic that one way to establish whether a particular dysfunction underpins a particular illness is to treat the individual for that dysfunction and monitor for whether or not symptoms of the illness subside. This approach is particularly attractive when the presence or agency of the hypothesised dysfunction is difficult to establish, as is the case with some of those that have been hypothesised to underlie CFS.

As such, treatment studies have been used as a means of testing the validity of many different hypotheses regarding the factors that cause and maintain CFS. While there have been a large number of interventions investigated in CFS patients, relatively few trials have been conducted using the randomised, double blind placebo-controlled methodologies that enable a reasonable assessment of treatment efficacy. As is the case with most areas of CFS research to date, inconsistent applications of case definitions and an absence of objective clinical indices have complicated interpretation of the treatment literature (Wilson, Hickie, Lloyd & Wakefield, 1994). A further issue is the fact that the heterogeneity of patient populations makes for heterogeneity of treatment responses. While this is likely to reduce the power of studies to detect significant effects, it may mean that significant responses to treatment compared to placebo in even a relatively small portion of any patient group may be meaningful (Wilson et al., 1994). As such effects are often detected via post-hoc analyses, they will, however, always require replication before their validity can be established.
This aim of this section is to review studies from the CFS treatment literature with a view to establishing how they add to our understanding of the factors that contribute to the illness. Given that uncontrolled studies contribute very little, if anything, to such a discussion, this review has focussed largely on those investigations that have used appropriate methodologies. These studies have been divided into those that have used predominantly pharmacological means of intervening, and those that have used predominantly behavioural methods.

*Pharmacological Interventions*

**Anti-viral agents**

The rationale for the various pharmacological interventions trialed in CFS has generally arisen from one of the major areas of investigation of the pathophysiology of CFS. Earlier theories that held that CFS was related to persistent viral infection led one group to trial the anti-viral agent, acyclovir in 27 CFS patients with abnormal EBV serologies (Straus et al., 1988). Patients were cycled through courses of treatment with either acyclovir or placebo with 6-week observation periods before, between, and after treatments. Three patients were withdrawn from the study after developing acyclovir-induced nephrotoxicity. Although 11 of the remaining 24 patients demonstrated improvement with acyclovir therapy, a similar number (10) improved while undergoing
the placebo treatment. The authors concluded that acyclovir had no impact on CFS, with the improvements being due either to placebo effect or spontaneous remission.

An anti-RNA virus agent, poly(I)-poly(C12U), or Ampligen, has been reported to have had beneficial effects in CFS patients. In a placebo controlled trial with 92 CFS sufferers, Strayer et al. (1994) reported a significant, but relatively small improvement in ratings of functional capacity amongst sufferers treated with Ampligen, while the placebo group demonstrated no such improvement. In fact, the investigators reported evidence of physiological deterioration in the control group. Improvements in the active treatment group were also reported for cognitive functioning and reduced need for other medications. While the authors suggested their results provided strong evidence for a positive role for Ampligen in CFS, some aspects of the study and the drug itself necessitate caution in accepting such a position. Firstly, the lack of any treatment response in the placebo group is atypical of CFS treatment studies, and raises the possibility that patients and/or researchers were not adequately blinded to the treatment conditions. Second, concerns have been raised about the hepatic toxicity of Ampligen and other noted side effects such as severe abdominal pain and cardiac arrhythmia. These substantial unknowns regarding the safety of the drug would seem to significantly outweigh the relatively small treatment gains reported (Engelberg, 1996).

Another antiviral agent, amantadine, has been recently trialed in CFS patients.
Amantadine was originally used in the treatment and prevention of A2 Influenza, where
it was serendipitously discovered to have significant CNS effects, primarily via the blocking of the reuptake of dopamine (Bowman & Rand, 1980). Amantidine was of interest for the treatment of CFS, as it has been reported to have beneficial effects on the fatigue of multiple sclerosis sufferers (Engleberg, 1996). A study that reported the results of a trial of Amantidine in CFS patients did not use a placebo group, rather, a comparison of treatment with L-carnitine (Plioplys & Plioplys, 1997). Amantidine was very poorly tolerated, with only half of the original patient sample of 30 being able to complete the course. No significant improvement was noted in those who completed the trial. Although significant improvements were noted for trials involving L-carnitine (Plioplys & Plioplys, 1997), the lack of a placebo comparison limits any conclusions that can be drawn.

Given that there is no convincing evidence that CFS is due to the persistence of viral infection in the first place, the lack of any substantial clinical gains demonstrated in these studies suggests that antiviral agents are unlikely to be effective in the treatment of the disorder.

**Immune modulators**

Other researchers, working from the perspective that CFS may be a disorder of immune regulation, have investigated the use of various immune modulators. As has been mentioned in an earlier section of this review, two groups simultaneously published
conflicting results with respect to the use of gamma globulin (IgG) in CFS in 1990 (Lloyd et al., 1990; Peterson et al., 1990). Peterson et al. (1990) found no appreciable benefit of intravenous (IV) administration of 1g/kg of IgG in 30 CFS patients compared to administration of an IV placebo preparation. In contrast, Lloyd et al. (1990) reported that blinded physician assessment indicated improvement in 43% of patients who had received 2g/kg IV IgG compared to improvement in only 12% of placebo treated controls. However, various other outcome measures, including assessment by a psychiatrist failed to differentiate between groups. Whether the differences in findings between these two groups were due to the differences in dose, patient group, relatively small sample size or problems in blinding due to the occurrence of side effects, is unknown. To some extent, however, it is no longer a significant issue, as a more recent and thorough dose ranging study carried out by the Australian group on a large sample found no evidence of benefit from IgG treatment (Vollmer-Conna et al., 1997).

The Australian researchers have also trialed the use of Dialyzable Leukocyte Extract (DLE) in CFS patients (Lloyd et al., 1993). The rationale for this trial was that DLE had been shown to be capable of transferring delayed-type hypersensitivity in humans and had been used extensively in disorders in which defective cell-mediated immunity was known to occur. The testing of DLE as a possible alternative to IgG was motivated by its comparative ease of administration, reduced side effect profile and substantially lower cost. The placebo-controlled trial included the use of DLE in combination with, and in comparison to, a six-session program of Cognitive-Behavioural Therapy (CBT).
Results indicated that DLE and CBT, either alone or in combination, delivered no greater benefit than normal clinical care.

Other immune therapies have also been trialed. See and Tilles (1996) conducted a placebo-controlled study of the use of interferon-α in 30 CFS patients. Four patients were withdrawn from the study due either to significant complications arising from treatment or intolerable worsening of symptoms. Although the authors reported a significant benefit of treatment in a particular subgroup of 7 patients who had reduced NK function, overall no benefits of treatment with interferon-α over placebo were apparent. Another study tested the use of the antihistamine terfenidine, administered orally to 30 patients (Steinberg et al., 1996). The authors found no change in various measures of physical and social functioning as a result of intervention, and concluded that terfenidine is unlikely to be of benefit in CFS. As the research stands so far, this conclusion can probably be extended to immunotherapies in CFS in general.

Psychotropic medications

While antidepressant medications have commonly been prescribed for patients with CFS, controlled trials of the therapeutic utility in the disorder have been conducted only in recent times. Psychotropic agents in general are indicated in CFS patients primarily because of the previously discussed high rates of psychiatric morbidity in this population. However, another fact that motivates the study of the use of antidepressants
in CFS patients is that they appear to have utility in the treatment of many of the
symptoms that are prevalent in CFS sufferers, such as sleep disturbance, generalised
pain, allergic reactions, gastrointestinal disturbance and headaches (Demitrack, 1996).
In contrast to the CFS literature, a number of placebo controlled trials of the use of
antidepressants in the symptomatically similar condition of fibromyalgia (FM) have
been carried out. These studies have indicated that some agents, most notably the
tricyclic antidepressant, amitriptyline, produce significant improvements in a proportion
of FM patients in areas such as pain, tenderpoints and sleep quality (Carette, McCain,
Bell & Fam, 1986; Goldenberg, Felson & Dinerman, 1986; Scudds, McCain, Rollman &
Harth, 1989).

The recent trials of antidepressants in CFS patients have focused on newer generation
psychotropics, such as the selective serotonin re-uptake inhibitors (SSRIs) and mono-
amine oxidase (MAO) inhibitors. A placebo controlled trial of the SSRI fluoxetine was
carried out in 44 depressed and 56 non-depressed CFS sufferers (Vercoulen et al., 1996).
Patients were administered either placebo or a 20mg fluoxetine dose daily for 8 weeks,
and assessed on a range of measures including activity, quality of life, depression,
cognitive functioning and others. The investigators found no change on any of these
measures that could be attributed to fluoxetine administration. Somewhat surprisingly,
this included a lack of impact on depressive symptomatology, leading the authors to
suggest that the processes underlying symptoms might be different in CFS patients than
in sufferers of major depressive illness.
A more recent trial of fluoxetine alone and in combination with a graded exercise program also found that the drug was unable to produce significant improvements in CFS patients (Wearden et al. 1998). While a modest antidepressant effect was found at 12 weeks, this had disappeared at 26 weeks. No significant improvements on any other measures at any time point were noted for fluoxetine treatment. The authors suggested that fluoxetine may have had a more substantial effect if the dosage had been able to be tailored to patients' individual needs, and if the sample had contained a higher proportion (than the 10%) of CFS sufferers who were comorbidly depressed. Although it had a higher drop out rate, graded exercise, on the other hand, produced significant (analyses based on intention to treat) reductions in the proportion of patients with case level fatigue and led to a 10% increase in functional work capacity.

Two small preliminary trials of the MAO inhibitors have been conducted by a group in the USA, both of which reported small but significant improvements in CFS patients. The first of these investigated the use of the nonspecific MOA inhibitor phenelzine in a group of 15 patients compared to placebo treated controls (Natelson et al., 1996). The findings of improvements on several clinical measures in the active treatment group are tempered by their small magnitude and the fact that six of the 15 active treatment patients dropped out of the trial. The second trial, in which the investigators administered selegiline, a MAO inhibitor that is largely selective for MAO-b, resulted in some significant improvements in 19 of the 25 patients who completed treatment
(Natelson et al., 1998). Again, small treatment effects in a small number of patients means that these results can only be taken as preliminary to further work.

As it stands, although there is the suggestion that some tricyclic antidepressants may have some utility in the treatment of pain and sleep disturbance, the utility of psychotropic interventions for the treatment of symptoms associated with CFS other than mood disturbance remains uncertain.

**Dietary supplementation**

Several studies have tested dietary supplementation in CFS. Cox, Campbell and Dowson (1991) reported a deficiency of red blood cell magnesium in CFS patients, and a significant improvement following a course of magnesium injections in 12 of 15 patients compared with 3 of 17 who improved in the placebo group. While these results were impressive, a larger study later found no evidence of magnesium deficiency in 96 CFS patients and concluded that the use of magnesium supplementation was unwarranted (Hinds, Bell, McMaster & McCluskey, 1994). Another highly positive report for the effect of a dietary supplement was published with respect to the administration of essential fatty acids in 63 post-viral fatigue patients (Behan, Behan & Horrobin, 1990). At one month, 74% of patients on the active treatment had improved, compared to only 23% of placebo treated participants. At three months, the gap between treatment and placebo effects had widened further, with 83% of active and 17% of
placebo patients reporting improvements. Although promising, these results applied to a specific group of patients that may not be representative of CFS in general, and they have not been able to be replicated (McCluskey, 1993). A small trial of liver extract-folic acid-cyanocobalamin reported a strong placebo effect with no additional benefit of active treatment (Kaslow, Rucker & Onishi, 1989), while another study also found no significant active treatment effect for multi-vitamin and mineral supplementation (Martin, Ogston & Evans, 1994). In summary, there is no evidence to indicate that dietary supplementation has any significant therapeutic impact in most people with CFS.

Corticosteroid supplementation

The recent shift in the focus of a number of investigators to HPA axis function in CFS has led to the trial of the administrating of corticosteroids. McKenzie et al. (1998) employed a low daily oral dose (16mg/m² of body surface area) of hydrocortisone for 12 weeks using a double-blind placebo control protocol with 70 CFS patients. Strong trends were apparent for small improvements in self-rated wellness in the active compared to placebo treatment groups, although various other measures did not differ. Evidence of adrenal suppression in a number of patients suggested that hydrocortisone treatment at the dose applied, at least, could cause more harm than benefit. A more recent crossover trial using a lower daily dose (5-10mg orally) reported more encouraging results, with a significantly greater reduction in fatigue scores being demonstrated by patients during the active treatment phase, and no evidence of adverse
effects (Cleare et al., 1999). The authors suggested that a proportion of CFS sufferers might benefit from low dose corticosteroid therapy, at least in the short term. Another preliminary crossover trial, this time of the mineralocorticoid agent, fludrocortisone, found no appreciable benefits of active over placebo treatment in 20 CFS patients who were completed both stages of the study (Peterson et al., 1998). These mixed results suggest that further research is required before judgements can be made about the effectiveness of corticosteroid supplementation in CFS.

**Behavioural Interventions**

The rationale for the use of behavioural interventions is based around models of the illness in which precipitating stressful life events, including episodes of illness, interact with individual susceptibilities to shape beliefs that drive avoidance of physical and mental activity which, in turn, leads to the perpetuation of the disorder (Butler, Chalder, Ron & Wessely, 1991; Surawy, Hackmann, Hawton & Sharpe, 1995). Behavioural interventions, such as Graded Exercise programs and Cognitive-behaviour therapy (CBT) for CFS, therefore, focus on challenging the cognitive distortions and illness beliefs that promote avoidance behaviour, and improving patients' sense of control over their symptoms. Patients are encouraged to recommence activities in a controlled fashion, so as not to overtax their deconditioned systems and thereby reinforce the beliefs which fuel avoidance in the first place. Rather, the aim is for patients to be able
to gradually re-extend their boundaries regarding what they can and cannot safely do (Butler et al., 1991). The major difference between CBT and Graded Exercise programs for CFS is that, while CBT uses both cognitive and behavioural techniques to address faulty cognitions and increase activity levels, Graded Exercise simply entails a program of controlled exercise, and relies on the patients' positive experiences to reinforce the benefits of a more active lifestyle.

In recent years, a number of well-controlled studies have been conducted to test the benefits of behavioural interventions.

**Graded Exercise**

Two studies have trialed the use of graded physical exercise programs in CFS patients. The first of these, by Fulcher and White (1997), compared the efficacy of a graded aerobic exercise treatment with that of a combination of flexibility and relaxation training. CFS patients meeting the British criteria were recruited for the trial, although patients who demonstrated psychiatric or sleep disturbances were excluded. Both programs involved weekly sessions for 12 weeks and prescribed routines at home that patients were encouraged to perform at least 5 days per week. Aerobic programs, which mostly entailed walking, were tailored to individual patients, starting at between 5 and 15 minutes of work at 40% of peak oxygen consumption, then increasing by 1-2 minutes per week up to a maximum of 30 minutes. Once the 30 minute stage had been reached,
intensity was increased gradually to a maximum of 60% of peak oxygen consumption. Flexibility training involved stretching and relaxation techniques starting at 10 minutes per day and building to 30 minutes.

Of the 33 patients allocated to each group, 16 reported feeling either much better or very much better at 12 weeks in the aerobic group compared to 8 of the flexibility training group. This difference only just qualified as statistically significant. Drop out rates were similar for both treatments, and only two patients, one from each group, reported feeling worse as a result of the intervention. Perhaps surprisingly, there appeared to be no association between improvements in aerobic capacity and self-reported improvement. While significant improvements were reported for a number of physiological and self-report variables, such as total fatigue, physical functioning etc., these were obtained by the use of multiple comparisons with no apparent adjustment to the Type I error rate. Treatment gains appeared to be long-term, with 74% of the 52 participants who responded to a 12-month follow-up survey reporting that they felt ‘better’. Because members of the flexibility group were able to cross to the aerobic program after the initial 12 weeks, no meaningful data were available to assess long-term outcome in patients treated this way.

It has been suggested elsewhere (Deale, Chalder & Wessely, 1998a; Wessely et al., 1998) that the lack of relationship between objective measures of improvements in physical fitness and self-rated reductions in fatigue, supports the view that disability is
more related to behavioural avoidance and confidence than physical fitness per se. While this may be true to some extent, finding support for it from the Fulcher and White (1997) study relies on the assumption that aerobic exercise promotes confidence and reduces avoidance more than is the case in flexibility and relaxation training. The logic of this assumption is unclear, and the empirical data required in order to evaluate it are lacking. Another possible mechanism for improvements via exercise has been suggested in the context of the recent interest in HPA axis dysfunction in CFS. Scott and Dinan (1999) have noted that exercise is one of the most potent activators of HPA function and, as such, may act directly on the pathophysiological underpinnings of the disorder. While the findings of Fulcher and White (1997) are promising, they require replication in patients more representative of CFS sufferers in general. At the very least, they offer strong evidence that physical exercise, properly managed in CFS is not harmful.

The only other controlled trial of exercise therapy in CFS, which has already been mentioned, is the randomised trial of aerobic exercise alone and in combination with fluoxetine (Wearden et al, 1998). The exercise program entailed at least three 20-minute sessions per week over six months. Intensity was originally set at 75% of peak oxygen consumption, and increased only when clear fitness objectives were attained. While 25 of 67 patients dropped out of the exercise conditions, analysis on the basis of intention to treat still found significant benefit in terms of functional work capacity, an objective measure of aerobic fitness. Exercise also produced trends towards a decline in fatigue scores, although these did not attain statistical significance. Unlike the Fulcher and
White (1997) study, objectively measured physical improvements (functional work capacity) were significantly, although only moderately, correlated with reductions in fatigue scores. In discussing the relatively moderate improvements noted in this study compared to Fulcher and White (1997), Deale et al. (1998) pointed out that encouraging outcomes from clinical trials conducted under strictly controlled conditions in selected patient samples may not translate well when treatments are put into practice under more realistic clinical situations, with more representative patient samples and program resources.

**Cognitive-Behavioural Therapy**

Several trials of cognitive-behavioural therapy (CBT) have also been conducted with CFS patients. As alluded to earlier, CBT focuses on challenging the cognitive distortions and illness beliefs that promote avoidance behaviour, and improving patients’ sense of control over their symptoms. Patients are encouraged to recommence activities in a controlled fashion, so as not to overtax their deconditioned systems and thereby reinforce the beliefs which fuel avoidance in the first place. Rather, the aim is for patients to be able to gradually re-extend their boundaries regarding what they can and cannot safely do (Butler et al., 1991).
Two early uncontrolled trials provided somewhat conflicting indications as to the likely benefits of CBT in CFS. Butler et al. (1991) reported that of 27 patients who completed therapy (18 refused CBT as an option and 5 dropped out), 22 reported feeling better or much better, and only 1 patient experienced a worsening of symptoms. Persistent mood disorder and strength of physical attributions predicted poor outcome. A later study compared a group of CFS sufferers treated via CBT with an untreated CFS group and another group of patients suffering from major depression (Friedberg & Krupp, 1994). This study reported trends but no significant treatment gains for the treated CFS group. However, the subgroup of CFS patients with depression did evidence significant reductions in depression, stress, and fatigue severity. Patients in the major depression group also experienced significant reductions on these parameters, and the authors suggested that CBT might therefore only be active in CFS where there are significant comorbid depressive symptoms. Other writers in the area have pointed out that the CBT protocol employed was focussed on coping with the illness, rather than on challenging illness beliefs and behaviours seen as contributing to the perpetuation of symptoms (Chalder, Deale & Wessely, 1995; Sharpe, 1996). Chalder et al. (1995) have also criticised various procedural and methodological aspects of the study, such as the brevity of treatment (6 sessions) and non-random group allocation.

The first placebo controlled investigation of a psychological intervention in CFS was carried out in Australia by Lloyd et al. (1993). This study, which has been outlined in the immunological treatments section, compared CBT treatment with the administration
of the immune modulator, DLE, a placebo group and another group on standard clinical management. CBT involved 6 sessions of between 30 and 60 minutes duration conducted biweekly. Treatment focussed on challenging patients’ self-perceptions of being at the mercy of their illness through discussion and education. A graded exercise program was tailored for each individual and patients were encouraged to carry out the program at home. Individual issues with respect to difficulties that arose in the implementation of the program were addressed via a collaborative problem solving approach. Results of the trial indicated that CBT, either alone or in combination with DLE, provided no benefit over normal clinical management. Although this study offered no support for the use of CBT in CFS, the treatment was brief and the authors themselves indicated that the program might have lacked the intensity required to produce changes.

The two most recent randomised, controlled trials of CBT in CFS, which have both employed programs of substantially greater intensity, have reported significant positive effects. The first of these (Sharpe et al., 1996) randomly allocated 60 consecutively referred CFS patients to either normal medical care or medical care plus 16 one hourly sessions of CBT. Two outcome goals were set with respect to Karnofsky performance ratings. The first was the achievement of a score of 80, which represents normal functioning (with effort and some signs and symptoms of disease), while the second was an improvement of 10 points, which was regarded as clinically significant. All patients offered treatment accepted and completed the program. At 5-month follow up,
differences in outcome measures were small and nonsignificant. By 12 months, however, 22 of 30 patients in the CBT group had achieved a normal Karnofsky rating, compared with only 8 of 30 in the standard care group. This difference was highly statistically significant. Similar results were obtained for patients in the two groups who had made a clinically significant improvement. Although complete resolution of symptoms only occurred in a few patients, and treatment conditions were unbalanced, in that patients from the CBT group received substantially more treatment than those in the medical care only group, these results are impressive, and unprecedented in the treatment literature for CFS. Importantly, the participants were likely to be representative of CFS sufferers generally, in that they were consecutive referrals and not excluded on the basis of comorbid mood or sleep disturbances. A possible problem with respect to generalisability is that patients were, on average, relatively short term sufferers (17 months) and moderately disabled (Gibbons, McIntyre & Richards, 1996).

A similar study of 60 CFS patients, comparing CBT with relaxation, also reported significant gains following CBT (Deale, Chalder, Marks & Wessely, 1997). The same number of treatment sessions was conducted for both groups. Main outcome measures were significant clinical improvement (increase of 50 points) or an end score of 83 on the Medical Outcomes Study Short-Form General Health Survey (Stewart, Hays & Ware, 1988). Seven patients deemed as eligible for the study refused treatment and a further seven CBT and four relaxation patients dropped out during the program. After six months, 19 CBT and seven relaxation patients had improved to the standards
specified a priori. This difference was significant on an intention to treat basis, with dropouts classified as unimproved. Improvements were also of a greater magnitude within those classified as improved via CBT compared to improved relaxation patients. A particular strength of this study was that, unlike Sharpe et al. (1996), the researchers compared two psychological interventions of similar intensity. Interestingly, a companion paper outlining characteristics associated with improvement reported that physical illness attributions assessed prior to treatment were not related to outcome (Dcalc, Chalder & Wessely, 1998b). These attributions did not change with treatment, even in those patients who improved, although beliefs about the avoidance of exercise and activity in general did. This is perhaps explainable in that physical attributions may make avoidance of activity more likely, but once such avoidance is overcome, physical attributions are irrelevant. Also, improvements associated with exercising and being more active do not preclude physical causes.

More research is required to assess which components of the above programs produced the improvements, and whether the application of CBT in the types of real-world clinical settings in which most clinicians and patients operate remains a practical and effective option. Of course, it must also be recognised that a proportion of patients in both trials did not achieve significant improvement, and very few could be regarded as completely recovered. Whether this indicates that CBT operates by improving patients’ abilities to adapt to underlying pathological processes, or whether it goes some way to addressing those processes directly is yet to be established. Even if some of the processes of this
multifactorial syndrome are not addressed by CBT, however, it would seem that the
treatment does address at least some important aspects that lead to disability.

**Contribution of Treatment Research to the Question of Aetiology**

Conceptualisations of CFS as an infectious process or as a disturbance of immunity are
weakened by the lack of significant treatment effects achieved via the use of antiviral
agents and immune modulators. Similarly, the ineffectiveness of the various
psychotropic agents trialed with CFS patients provides further evidence that CFS is
qualitatively different from mood and anxiety disorders. The small treatment effects
achieved through corticosteroid supplementation offers some support for the hypothesis
that HPA-axis disturbance plays a role in the pathology of CFS, although the lack of
substantial impact would suggest that this role may not be as central as has been
proposed (Demitrack et al., 1991).

In the absence of any reliable findings of improvements associated with these
pharmacological interventions, the repeated demonstration of the benefits of CBT in
CFS patients indicates that CBT is, to date, the most clearly effective treatment available
for the disorder. The relative success of CBT offers support for theories of CFS that
emphasise a role for cognitive distortions and subsequent avoidance of physical and
mental activity in the maintenance of the disorder (eg Butler et al., 1991; Surawy et al.,
1995), without precluding the possible contribution of other factors, such as precipitant infection, immune dysregulation and HPA-axis dysfunction. The superiority of such a multifaceted treatment approach over unidimensional approaches, whether they be pharmacological or exercise oriented, confirms the view that CFS is the product of a complex interaction of a number of factors (Demitrack, 1996; Thomas, 1993; Wessely et al., 1998; Wilson et al., 1994).

**The Reconceptualisation of CFS**

The questions surrounding the aetiology and underlying pathophysiology of CFS have been approached from many different directions. This chapter has provided an overview of the main approaches, which have conceptualised CFS variously as the result of an infective process, immunological dysfunction, psychiatric disorder, or as a primary disturbance located somewhere within the CNS. None of these approaches, on its own, has been able to provide a complete and convincing account of the processes that underlie the development and maintenance of CFS. However, all of the approaches could validly claim to have some explanatory power in at least a proportion of cases.

In the last five years, a considerable shift has occurred in the way that CFS is conceptualised. While much of the research reviewed in this chapter has been motivated by the search for a single aetiological agent or pathological process that underpins the disorder, it has become increasingly clear that CFS is a complex condition that is
**Figure 3.1** Two hypothetical models of the interaction of diverse factors in the development and maintenance of CFS. The model on the left, adapted from Demitrack (1996) posits that the interaction of various predisposing and precipitating factors triggers HPA-axis dysfunction, which is then maintained by various perpetuating factors. The model on the right, adapted from Fox and Cleare (1998), posits that the interaction of predisposing and precipitating factors results in acute or subacute fatigue, which, due to the impact of various perpetuating factors does not resolve, and becomes CFS.
unlikely be explained using a unidimensional approach (Demitrack, 1996; Thomas, 1993; Wessely et al., 1998; Wilson et al., 1994). Rather than a discrete disease entity, CFS is coming to be seen more as a clinical condition in which a diverse range of factors combine to produce the symptom complex that defines the observable clinical syndrome (Demitrack & Abbey, 1996).

Drawing on the body of research into the aetiology and pathophysiology of CFS, Demitrack (1996) and Fox and Cleare (1998) have summarised these factors in hypothetical models of CFS (Figure 3.1). Both models divide factors into those that predispose, precipitate and perpetuate the symptom complex. Both models also clearly entail a diathesis-stress view of the development of the disorder, and acknowledge that the factors that predispose an individual to the disorder, as well as those that precipitate and maintain it, arise from physiological, psychological and social domains. Importantly, while such models provide fertile ground for the generation of research questions pertaining to the study of CFS, they emphasise the necessity of adopting a multidimensional, biosocial approach to its investigation and treatment.

Of course, such an approach does not deny the need to reduce complex problems down to the study of their component parts: it simply provides a context from within which to put the pieces together. The remainder of this thesis is concerned with the investigation of one set of factors, circadian timing, that may contribute to the overall process that leads to the generation and maintenance of CFS. The following chapter provides a rationale for such a focus.
CHAPTER 4

RATIONALE FOR THE INVESTIGATION
OF THE CIRCADIAN TIME-KEEPING SYSTEM
IN CFS
The aim of the preceding three chapters has been to provide an overview of the historical and scientific influences that have shaped the way that CFS is currently defined and understood. This was done to provide a context from within which to develop a rationale for the study of the circadian time-keeping system in CFS patients, which is the primary aim of this thesis. Recently published theoretical and empirical work has indicated that circadian dysregulation could be one of the factors that contribute significantly to the aetiology and/or maintenance of the syndrome. However, systematic studies of the circadian time-keeping system in CFS sufferers are lacking. Prior to reviewing this work and interpreting its significance, it is necessary to provide an overview of the circadian time-keeping system.

The first aim of this chapter is to outline the basic properties, function and physiology of human biological rhythms in general and circadian, or daily rhythms specifically. The second aim is to describe the importance of the circadian system to healthy functioning, and its known role in various states of ill health. The third part of this chapter will present a rationale for the study of circadian rhythmicity in CFS, along with a review of work in the area to date. Finally, a proposal for the systematic study of circadian factors in CFS will be presented.
The Rhythms of Life

The astronomical forces impinging on the Earth ensure that our environment is pervaded by pronounced, regular cycles of various kinds. The Earth rotates on its axis about every 24 hours, resulting in a regular day-night cycle. The Moon revolves around the Earth every 27.3 days, resulting in approximately monthly lunar cycles. Because the Moon revolves around the Earth in the same direction as the planet spins, the Earth has to rotate slightly more than once (373 degrees) for the same longitude to face the Moon again (Kaufmann, 1987). Thus, the lunar “day” is slightly longer than 24 hours (24.8). The gravitational pull of the Moon acts on the oceans of the Earth to produce tidal cycles, twice every lunar day. The Earth itself is a satellite of its star, Sol, circling it in just over 365 days. The combined forces of gravity from the Sun and Moon, and the spinning of the Earth tilt the planet’s axis 23.5 degrees from perpendicular to the ecliptic plane (Kaufmann, 1987). This, in turn, means that at different points in the Earth’s circumnavigation of the Sun, the northern and southern hemispheres receive different levels of exposure to its light, heat and radiation; both in terms of intensity and length of time. The result of this is a yearly cycling of weather and lighting conditions, or seasons, which become more pronounced as one travels away from the equator.

Everything that lives and has lived on the Earth has evolved through cons of these same cyclic patterns. It is unsurprising, therefore, to find that these patterns are reflected in the physiology and behaviour of virtually all living organisms. However, it has only
been in the last few centuries that people have noticed the intrinsic and pervasive presence of 'biological rhythms' in living systems, and only in the last few decades has their basic importance to life and health begun to be realised.

**Basic Properties of Biological Clocks.**

The fact that the activities of plants and animals vary rhythmically across days, months and seasons was obvious to people from very early times. There are written records that date from the marches of Alexander the Great in the 4th century B.C. documenting daily rhythms in the opening and closing of leaves and flowers (Moore-Ede, Sulzman & Fuller, 1982). However, until the eighteenth century, these cycles were quite reasonably assumed to be nothing more than passive responses to a cyclic environment. This interpretation was tested by French astronomer Jean Jacques d'Ortous de Mairan, who experimented with heliotropic plants in 1729. Heliotropes raise their leaves by day and lower them at night. When de Mairan isolated these plants in constant darkness, he found that they continued to open and close their leaves with the rise and fall of the sun (de Mairan, 1729). This was the first documented demonstration of the persistence of diurnal rhythms in spite of the lack of any apparent environmental time cues (Moore-Ede et al., 1982). A century later, Augustini de Candolle (1832) repeated and extended de Mairan's experiments and found that, although the rhythmic leaf movements persisted, they ceased to cycle at exactly 24 hours, instead varying at periods between 22 and 23 hours (cited in Moor-Ede et al., 1982). This made it very unlikely that the plant
was receiving time cues from any other naturally occurring environmental fluctuation, such a temperature, and was therefore very strong evidence that the plant possessed some kind of internal timing mechanism.

Since these early experiments, internally driven biological rhythms have been found to be a ubiquitous phenomenon, present throughout the plant and animal kingdoms (Moore-Ede et al., 1982). The fact that the presence of internal timing mechanisms has been found to be such a common feature of living things not only suggests that it must provide organisms with a fundamental adaptive advantage with respect to survival, but has also led some biologists to suggest that the awareness of time should be regarded as the sixth sense (Binkley, 1990).

The most obvious adaptive advantage provided by internal timing mechanisms is that they allow organisms to anticipate regularly recurring daily events, and to initiate appropriate physiologic and behavioural responses sufficiently in advance so that the optimal outcome will be obtained. In short, biological rhythms allow organisms to be prepared to take advantage (or limit the potential damage) of regularly occurring situations.

A less apparent, although no less important aspect of temporal organisation, is the coordination of the plethora of internal physiological systems. Physiologic and metabolic processes require internal sequencing so that interdependent processes are
coordinated, and incompatible processes are separated, in time (Moore-Ede et al., 1983a). Turek (1994) analogises the role of the circadian system with that of the conductor of an orchestra, coordinating the multitude of instrumentalists so that the result of their combined efforts is music rather than noise. He notes that a lack of synchrony (rather than symphony) within the internal physiological environment can lead to chronic difficulties and potentially severe consequences for the health and well-being of an individual.

**Terminology**

The 24-hour sleep/wake cycle present in most mammals including humans is probably the most salient of all biological rhythms, in the sense that it has many components that are both physiological and behavioural, and that, to a large extent, it dictates the organism's life style. Rhythms that vary around a 24-hour period are known as *circadian*, a term derived from the Latin for 'about a day'. Cycles that occur more often than once a day, such as heart beats or sleep cycles are referred to as *ultradian*. Rhythms that occur less frequently than every 24 hours, such as menstrual cycles are known as *infradian*, or are referred to as *circannual* if they occur around a period of a year, like the hibernation or breeding patterns of some animals.

As has been noted, the experiments of de Candolle (1832), outlined above, were particularly significant because they demonstrated that, in the absence of environmental cues, the rhythmic fluctuations noted in heliotropic plants tended to cycle around 22 or
23 hours, rather than the 24 hour cycles of the outside world. The tendency for plants and animals isolated from external time cues, to revert to their own species specific temporal cycle, which is either slightly more or slightly less than 24 hours, is a defining feature of endogenous circadian rhythms (Turek, 1994). This phenomenon is called free running. The length of a cycle is known as its period, or tau. In some species, including humans, the endogenous rhythm is set at slightly longer than 24 hours (Wever, 1986), so that when they are isolated from environmental cues their free run causes them to desynchronise with the external world by way of cycling later and later. Their rhythm is said to be phase delaying, because their cycle is delayed further compared to ‘real time’ each day. On the other hand some species, such as the heliotropes mentioned above, have an endogenous rhythm of slightly less than 24 hours (Binkley, 1990), so that when they free run, they cycle earlier and earlier compared to ‘real time’. In these cases, the rhythm is said to be phase advancing.

A final important property of biological clocks is their tendency to entrain to external stimuli. If an organism has been isolated from external time cues, and has subsequently been free-running at its own endogenous pace, and that organism is then returned to a cyclic environment, its rhythm will readjust so that it is synchronised with that environment (Moore-Ede et al., 1982). When this occurs, the rhythm is said to have entrained. The stimulus to which the rhythm entrains (the entraining agent) is often referred to as the zeitgeber, or ‘time giver’. Mammals, in particular, most readily entrain to a regular light-dark cycle, although if light is kept constant, they will entrain to other
regular stimuli, such as temperature or feeding schedules (Aschoff, 1981). Regardless of its regularity, however, terrestrial (as opposed to marine) organisms in general will not entrain to a cycle that is not close to 24 hours. Rats, for instance, will free-run when placed in environments cycling at less than 20 hours or more than 28 hours (Aschoff, 1981).

The Physiology of the Circadian System

Identification of the SCN as the Biological Masterclock

While the existence of an internal regulator for the multitude of rhythmic behavioural and physiological processes had been hypothesized for decades, it was not until the mid 1960s that scientists came close to identifying its location. Although he did not make the final discovery of the precise location of the internal circadian masterclock, the pioneering efforts of Curt Richter contributed greatly to the process. Richter (1965) used the free-running rhythm of laboratory rats as an indicator of circadian integrity, which he challenged with a broad range of metabolic, endocrinologic and neurologic insults in order to determine its basis. His numerous, unfortunate rodent subjects remained rhythmic despite being exposed to procedures involving the removal of various endocrine organs, including the pineal, undergoing electroshock treatment, prolonged anaesthesia, and alcohol intoxication. After lesioning hundreds of brain areas, Richter eventually narrowed the search to the hypothalamus. After another two
hundred or so hypothalamic lesions, Richter (1965) was able to demonstrate that single lesions in the anterior hypothalamus disrupted the circadian rhythmicity of activity, and drinking and feeding behaviour.

Richter’s methodology was too crude to more precisely define the location of the biological clock, and it was not until the early 1970s that techniques became sophisticated enough to go further. In 1972, Moore and Lenn used the newly developed technique of tract tracing via the use of tritiated amino acids to identify the retino-hypothalamic tract (RHT), extending from the retina and terminating in the suprachiasmatic nuclei (SCN) of the anterior hypothalamus. While Moore was apparently unaware of Richter’s work, he had theorized from other indirect evidence that the SCN might be involved in photoreceptive mediation of the neuroendocrine system (Weavcr, 1998). As such, he proceeded with a study in which the SCN was lesioned in order to determine the consequences for circadian rhythmicity. Meanwhile, Fred Stephan and Irving Zucker from the university of California, who were familiar with Moore and Lenns’ (1972) tract tracing studies, and with Richter’s (1965) earlier work, independently began similar research (Stephan & Zucker, 1972). Both groups had expected to find that the SCN was merely a relay point for photic information on the way to the biological clock and, as such, expected that SCN lesions would simply induce free-run. Instead it was found that the procedure totally abolished circadian rhythms of activity and drinking behaviour (Stephan & Zucker, 1972) and adrenal corticosterone (Moore & Eichler, 1972).
These seminal studies were the first identifying the SCN as the biological masterclock in mammals. Since then, several important works have established this point beyond reasonable doubt. The first of these showed that rat SCN isolated in vivo continued to fire rhythmically while other brain areas lost their circadian firing patterns (Inouye & Kawamura, 1979). In vitro studies confirmed the intrinsic circadian pattern of firing of SCN neurons (Green & Gillette, 1982; Groos & Hendriks, 1982; Shibata, Oomura, Kita & Hattori, 1982). Later, other researchers provided the somewhat remarkable finding that rhythmicity lost due to SCN destruction could be restored by the transplantation of fetal SCN tissue (Lehman et al., 1987). Even more remarkable, was the finding that the period of the rhythm restored corresponded to that of the donor, rather than that of the host (Ralph, Foster, Davis & Menaker, 1990). To date, although some tissues outside the SCN have been shown to have the capacity to oscillate autonomously, there is no strong evidence that any structure outside the SCN is capable of acting as a master circadian pacemaker in mammals (Turek, 1998).

*The Molecular Basis of Endogenous Circadian Rhythmicity*

The finding that individual neurons taken from mammalian SCN and maintained in dispersed cell culture continue to express circadian firing patterns that are independent of one another (Welsh, Logothetis, Meister & Reppert, 1995), indicates that circadian oscillation is a feature intrinsic to the biochemistry of its cells, rather than being an emergent property of the circuitry. As is commonly the case in research into the genetic
bases of various aspects of structure and function, elucidation of the molecular basis for
the rhythmic nature of SCN cells has been obtained from studies of *Drosophila*. Early
studies developed mutant strains of *Drosophila* in which eclosion and locomotor
rhythms differed from the usual near 24-hour cycle (Konopka & Benzer, 1971). Three
mutations were identified, including one strain that was arrhythmic and others with
periods that were either significantly shorter (19h) or longer (29h) than 24 hours. The
site of the mutation was identified as the *per* (for period) locus on the X chromosome.
Since then, several genes that are involved in the functioning of the circadian clock have
been cloned following their identification by such mutagenesis screening for altered
phenotypes. These include the timeless (*tim*) *dcl*ock and *double-time* genes in
*Drosophila* (Van Gelder, 1998), the frequency (*frq*) gene in *Neurospora* (Dunlap, 1996),
and the *Clock* gene in the mouse (Vitaterna, et al., 1994).

In *Drosophila*, the *per* and *tim* alleles operate in a self-sustaining negative feedback loop
in which the abundance and location of the proteins they express define circadian time.
These genes, which are active in the early part of the night, lead to the build up of *Per*
and *Tim* proteins in the cytoplasm throughout the evening. When concentrations of the
proteins are high enough, *Per* and *Tim* bind to form heterodimers, which are able to
permeate the nucleus. Once there, these heterodimers are able to suppress the
expression by *per* and *tim*, leading to the cessation of further *Per* and *Tim* production.
The suppression of *per* and *tim* continues until the heterodimers are broken down. The
entire process, which takes approximately 24 hours, then begins again (Hastings 1998;
Kennaway, 1998; Wilsbacher & Takahashi, 1988). Interestingly, recent studies have demonstrated that light exposure leads to the degradation of Tim, and this provides a likely mechanism for the entrainment of the Drosophila clock by the light-dark cycle (Lee, Parikh, Isukaichi, Bac & Edery, 1996; Myers, Wager-Smith, Rothenfluh-Hilfiker & Young, 1996; Zeng, Quian, Myers & Rosbash, 1998).

It is likely that this process is representative of the molecular basis of clock function in mammals, including humans. After the cloning of the Clock gene in the mouse, mammalian orthologs of per (mper1, mper2 and mper2) have been identified (Sun et al., 1997; Zylka, Shearman, Weaver, & Reppert, 1998). It appears that the Clock proteins dimerise with those of another allele, bmal (for brain and muscle ARNT-like factor) to provide positive drive to per, activating and promoting transcription (Wilsbacher & Takahashi, 1998). It is now known that the mammalian per orthologs are present in tissues outside the CNS, including skeletal muscle and testis, and this is strongly indicative of the existence of brain independent clock cells (Zylka et al., 1998). Interestingly, the rhythmic expression of period genes that exist outside of the brain has been found to be phase-delayed by up to 12 hours relative to those in the SCN (Sun et al., 1997; Zylka et al., 1998). This suggests that the SCN operates as the master mammalian pacemaker, at least in part, through the coordination of various autonomous oscillators throughout the body (Wilsbacher & Takahashi, 1998).
Synchronisation of the SCN with the Environmental Cycle

While, SCN tissue is capable of endogenously maintaining a regular cycle of firing of approximately but not exactly 24 hours, some mechanism by which it can be synchronized with the solar cycle is obviously required for this to be of adaptive utility. Given that circadian rhythmicity has evolved as an adaptation to the solar cycle, it is not surprising that light is the most salient entraining agent. In humans, the length of the endogenous circadian period is slightly longer than a solar day (Wever, 1986) and, as such, requires small daily phase advances in order to remain in synchrony with the ambient light-dark cycle.

In humans, as in other animals, the clock responds differently to light at different times of the (subjective) day. The differing responses of the clock at different times of day is charted as the phase response curve (PRC: Binkley, 1992). Apart from differences with respect to the intensities required, the human PRC to light is remarkably similar in nature to that of other mammals (Minors, Waterhouse & Wirz-Justice, 1991). That is, light pulses of sufficient intensity and duration will produce a phase delay in the SCN rhythm when administered immediately prior to the early morning core temperature minimum, which generally occurs just prior to waking. In contrast, exposure immediately following the occurrence of the core temperature minimum results in a phase advance (Minors et al., 1991). More substantial shifts are produced when light exposure is more proximal to the core temperature minimum, with little or no effect
when it is more than six hours either side (Minors et al., 1991). Thus, exposure to early morning light after waking provides the necessary curtailing of the longer than 24-hour endogenous rhythm of the human SCN in order for the individual to remain entrained to the ambient light-dark cycle (Wever, 1986). Exposure to light in the early evening may act as a further entrainment signal, perhaps by ensuring that the morning phase advance was not too large.

**Pathways of Photic Entrainment.**

Although there have been recent reports of extraocular photic entrainment of human circadian rhythms (Campbell & Murphy, 1998), most researchers agree that phototransduction for circadian purposes occurs primarily, if not exclusively, through the retina. The actual photoreceptors involved in transducing photic information into neural signals for the circadian system is unclear, although it is likely that they are specialised cone cells operating separately from the visual system and specifically tuned to detect photic conditions indicative of time of day (Rea, 1998). The excitatory amino acid, glutamate (Ding et al., 1994), appears to be involved in the communication between these photoreceptors and the clock, via the direct pathway that extends through retinal ganglia, along the RHT and terminates within the SCN (Moore & Lenn, 1971). Two other indirect pathways also carry photic information to the SCN, the geniculohypothalamic tract (GHT) which extends from the intergeniculate leaflet and the pretectohypothalamic tract (PHT), which projects to the SCN from the pretectal area (Rea, 1998). The RHT alone is both necessary and sufficient to produce photic
entrainment (Johnson, Moore & Morin, 1988; Moore, 1997). The GHT appears to play a modulatory role in photic entrainment (Pickard, Ralph & Menaker, 1987), and may also be a pathway for non-photonic entrainment (Janik & Mrosovsky, 1994). The role of the PHT remains unknown (Rea, 1998).

Glutamate itself may act primarily by facilitating intercellular movement of nitric oxide within the SCN (Ding et al., 1994) which, among other things, leads to the phosphorylation of transcription factors such as Ca$^{2+}$/cAMP response element binding protein (CREB) and the activation of immediate-early genes such as those from the fos and jun families (Gillete, 1998). It is known that c-fos and certain jun proteins bind to form heterodimers known as ‘activator proteins’ that, in turn, bind to specific DNA sequences to regulate the expression of target genes (Curran & Franza, 1988). Presumably, in the SCN, the targets are those genes that have been described above as being specifically involved in circadian rhythmicity, although the exact mechanisms are, as yet, unclear. It has been repeatedly demonstrated that light exposure will only induce Fos expression in the SCN during (subjective) night (Rea, 1998). Many of the details regarding the operation of these complex processes remains unknown, especially how the same stimulus can have the opposite effect, depending on the time of night.

Finally, the demonstration of serotonergic pathways extending from the raphe nucleus and terminating in the retinorecipient region of the SCN (Azmitia & Segal, 1978; Moore, Halaris & Jones, 1978; van de Kar & Lorcns, 1979) indicated that the clock might also
be regulated to some extent by serotonergic mechanisms (Azmitia & Segal, 1978). Rae (1998) reviewed various evidence of serotonergic modulation/inhibition of SCN neurons that suggested that serotonin (5HT) modulates photic responses in the SCN through at least two mechanisms. The first of these is the modulation of the response of SCN neurons to RHT stimulation through specialised 5HT subtype receptors, and the second entails the direct attenuation of RHT transmission to the SCN, probably through the inhibition of glutamate release. Thus, serotonergic mechanisms regulate both the flow of photic information to the SCN from the RHT, and the response of SCN neurons to it.

**Non-photic Regulation of the SCN**

While it is clear that the light-dark cycle is the most salient entraining agent in synchronising the intrinsic circadian rhythm of the SCN with that of the environment (Duffy, Kronauer & Czeisler, 1996), some non-photic stimuli also produce entrainment when lighting levels are kept constant. In mammalian laboratory animals, phase alterations and entrainment can be achieved by regulating the timing of physical activity (Marchant & Mistlberger, 1996; Mistlberger, 1991a; Mrosovsky, Rccbs, Honrado & Salmon, 1989) and, to a lesser extent, food availability (Mistlberger, 1991b; Mistlberger, 1994). Just as single pulses of appropriately timed bright light can induce phase advances and delays, single episodes of induced activity through exposure to a novel running wheel (Mrosovsky, 1996; Turek, 1989) and behavioural arousal due to handling and saline injection (Hastings et al., 1992) have also been demonstrated as capable of
producing phase alterations. In hamsters, social interaction has also been demonstrated to be capable of eliciting entrainment (Mrosovsky et al., 1989).

Although much harder to study, the effects of such non-photic stimuli on the circadian system appear to generalise to humans. Periods of nocturnal exercise have been shown to induce phase delays in hormonal rhythms in human participants (Buxton et al., 1997; Buxton, L'Hermite-Baleriaux, Hirschfeld & Van Cauter, 1997; Van Reeth et al., 1994), and regular behavioural patterns and/or social interaction is enough to maintain entrainment in constant lighting conditions (Aschoff, Fatranska & Giedke, 1971). The fact that awareness of clock time is insufficient to prevent free-run (Middleton, Arendt & Stone, 1996) indicates that behavioural, rather than cognitive factors are critical.

While it appears that behavioural arousal in the form of physical activity is a common component across mammalian species in non-photic entrainment of the circadian system, it is unclear whether it is physical activity per se, or some correlate, such as internal motivation or arousal that is the active agent (Hastings, Duffield, Smith, Maywood & Ebling, 1998). The findings that the amount of physical activity is not precisely correlated with the size of phase shifts (Wickland & Turck, 1996) and that physical activity under cold conditions fails to produce phase shifts (Mrosovsky & Bicillo, 1994) indicates that other factors may be involved. Reports of phase alterations resulting from immobilisation of hamsters during their normal active period (Van Reeth,
Hinch, Tecco & Turek, 1991), provide even stronger evidence that physical activity *per se* is not the active component producing non-photic entrainment.

The physiological mediators of non-photic entrainment are not well understood. IGL lesions block the ability of the aforementioned non-photic cues to affect the timing of the SCN (Hastings et al., 1998), indicating that non-photic entrainment of the SCN occurs via the GHT. This logic is confounded to some degree by the fact that lesioning of the IGL also results in reductions in physical activity, however, such reductions are insufficient to account for the loss of ability to entrain to non-photic stimuli (Wickland & Turek, 1996). Administration of several pharmacological compounds, including benzodiazepines, serotonergic agonists and neuropeptide Y, can individually produce SCN entrainment that is blocked by IGL lesioning (Hastings et al., 1998), indicating that non-photic entrainment is mediated by several different neurotransmitter systems.

Another compound, melatonin, which is the major hormone produced and secreted by the pineal gland, has also been demonstrated to have an entraining effect in mammals (Redman, Armstrong & Ng, 1983), including humans (Arendt, 1998). Pineal production of melatonin is under direct control of the SCN, which also appears to be a major site of action for the hormone, where it may be responsible for modulating the clocks sensitivity to light and/or act to assist the coupling of individual oscillators within the SCN (Cassone, 1998). While melatonin is postulated to have a number of physiological roles, including that of an internal mammalian zeitgeber (Armstrong,
1989), there is no indication that it is involved in naturally occurring non-photic entrainment.

**Entrainment of the Internal Environment to the Rhythm of the SCN**

The entrainment of the SCN rhythm to the ambient light-dark cycle is, of course, only half the story. There also needs to be a mechanism or mechanisms that allow the numerous subordinate oscillators and systems within the body to synchronise with the SCN rhythm and, therefore, each other. The means by which the SCN coordinates the plethora of circadian cycles of the internal environment remains largely unknown, particularly for humans. Evidence from animal studies suggests, however, that internal synchrony is achieved through a combination of neural and diffusible signals that emanate from the masterclock (LeSauter & Silver, 1998).

Studies of the rat and hamster SCN indicate the existence of four major efferent neural pathways from the clock that project to various areas of the hypothalamus (Miller, Morin, Schwartz & Moore, 1996; Swanson & Cowan, 1975). As might be expected, and lesion studies confirm, each of these pathways regulates the timing of different aspects of physiology. Early studies that transected all neural efferents from the SCN reported the abolition of behavioural rhythms of locomotor activity, drinking, as well as physiological rhythms (Stephan & Nunez, 1977), although some individual animals retain some aspects of rhythmicity in some functions (Honma, Honma & Hiroshige, 1984). Later studies using more precise lesioning techniques, however, showed that
neural isolation of the SCN from the rest of the brain did not abolish locomotor rhythms (Hakim, DeBernardo & Silver, 1991). It has since been suggested that imprecision of techniques employed in earlier studies may have led to the abolition of locomotor rhythms via the inadvertent damaging of the SCN itself (LeSauter & Silver, 1998).

The significance of the more recent studies is that they suggest that the SCN communicates with the internal environment via both neural and non-neural means, and that non-neural signals, in particular, are involved in the generation and entrainment of locomotor rhythms. Studies that have transplanted SCN tissue into animals that have had their own SCN removed and are subsequently arrhythmic, support this position in that locomotor, but not endocrine, rhythms are restored (Bitman, Matsumoto, Markuns, Meyer & Jetton, 1994; DeCourcey, & Buggy, 1989; Lehman et al., 1987).

Even these studies, however, are not conclusive with respect to the existence of non-neural control of locomotor activity by the SCN, because it cannot be unequivocally demonstrated that neural efferents do not regenerate to some degree. Conclusive evidence is available, however, due to the use of a technique in which grafts are encapsulated to allow the flow of nutrients and diffusible molecules between the transplanted SCN tissue and the host brain, but preclude the development of neural connections. Transplantation of encapsulate foetal SCN into hamsters restored locomotor activity rhythms that corresponded to the period of the donor rather than the host (Silver, LeSauter, Tresco & Lehman, 1996). This provided unambiguous support
for the idea that the SCN regulates some aspects of internal timing via a non-neural
diffusible signaling mechanism or mechanisms. Neither the nature of this signal, nor its
method of release and transmission are known. Possible transmission pathways include
passive diffusion into extracellular space, paravascular fluid pathways along blood
vessels, capillaries and venules, and diffusion through cerebrospinal fluid (LeSauter &
Silver, 1998). Further research is required to identify the substance(s) involved, its
mode of action, and physiological target(s).

Finally, the possibility that direct neural SCN control of the production and release of
melatonin by the pineal gland is another means by which the SCN synchronises bodily
systems has also been raised (Armstrong, 1989). Various evidence supports a role for
melatonin in the regulation of circadian functioning in general (Cassone, 1998) and
specifically, such as the circadian organisation of the immune response (Cardinali,
Brusco, Cutera, Castrillon & Esquifino, 1999). Such a mechanism adds a further
dimension to the study of SCN signalling pathways, in that it constitutes a neurally
mediated diffusible signal.

The Adaptive Significance of Temporal Organization in Humans

Broadly speaking then, circadian synchrony occurs on two levels. The first level is the
synchronization of the rhythm of the biological master-clock with that of the ambient
light-dark cycle or, at least, the 24-hour cycling of the social environment. This is
referred to as external synchrony. The second level is the synchronisation of the plethora
of cyclic functions of physiology and behaviour within each individual. This is achieved by having each of these entrained to the rhythm of the master clock and is referred to as *internal synchrony*. When both external and internal synchrony are achieved, then all component rhythms of the system are entrained to each other and to the environmental cycle.

Such a state promotes the well-being of the individual on many levels (Binkley, 1992; Moore-Ede et al., 1983a; Turek, 1994). First, appropriate timing of the sleep-wake cycle, the most apparent of human circadian rhythms, has the obvious practical value of ensuring that, as a diurnal species, we are active during the day and inactive at night. As well as it being easier to be active during the light, the fact that most people operate on this cycle facilitates social interaction and cooperation. Rhythms of food and liquid intake, and of waste expulsion tend to occur during the active period, allowing us to have a consolidated sleep period.

Less apparent, but just as important, are the benefits of synchrony between behavioural and physiological systems and physiological systems themselves. For instance, sleep itself is known to be of better quality and longer duration when it occurs during the descending limb of the core temperature rhythm, relative to sleep occurring at other times (Dijk & Czeizler, 1995). This phase of the core temperature rhythm occurs between the middle of the subjective evening and late in the subjective night (Refinetti & Menaker, 1992). Several studies demonstrate that regular meal timing results in the
entrainment of metabolic events such as cholesterol synthesis (Cella, Van Cauter & Schoeller, 1995), and the production and release of various digestive enzymes (Connor-Johnson, 1991). The anticipation of food intake by the circadian system thus allows for a more efficient digestive process. An example of the importance of the coordination of physiological rhythms lies in the inverse relationship between circadian variation of immune parameters, such as T- and B-lymphocyte levels and corticosteroids. The circadian variation of lymphocytes and other immune factors is coordinated so that much of the work of the immune system occurs during sleep (Abo, Kawate, Itoh & Kumagai, 1981), which is, reasonably, a time when levels of the immunosuppressive corticosteroids are at their nadir. The circadian surge of cortisol that occurs just prior to, or around waking, coincides with, and is instrumental in, the decline in lymphocyte levels and general immune activity (Abo et al., 1981). The functional advantage of such temporal organisation is that various immune functions occur in a coordinated, unimpeded and, therefore, efficient fashion at a time of relative physiological quiescence. Other rhythmic processes then ensure that these functions are switched off as the individual wakes and requires energy for the physical activity associated with competing for and metabolising nutrients and, in days past, avoiding becoming a source of nutrients oneself.

These examples are but a few of the multitude of adaptive temporal relationships between behavioural and physiological systems that are required to maintain the health
of an individual. Some well-known examples of what happens when such temporal coordination breaks down will now be reviewed.

**Disorders Associated with the Circadian System in Humans.**

In general, disorders that are known to be associated with disrupted circadian functioning can be divided into two categories: 1. those that are due to sleep-wake or lifestyle patterns that undermine proper entrainment between environmental, sleep-wake and physiological rhythms and, 2. those that are due to abnormal functioning of the clock. The aetiology and clinical significance of circadian disturbances in psychiatric disorder and older age remains unclear, and it is possible that both clock dysfunction and lifestyle factors contribute to their occurrence.

**Circadian Disorders Due Mainly to Lifestyle Factors**

**Jet Lag**

The most well known and commonly experienced disorders related to circadian functioning are those resulting from lifestyle patterns, namely jet lag and shift work related syndromes. Jet lag is a state of temporary internal and external desynchrony associated with rapid travel across several time zones. The symptoms of jet lag, which
can include; sleep disturbance, exhaustion, concentration difficulties, constipation or diarrhea, headaches, loss of appetite and visual disturbances (Ehret & Scanlon, 1983), are mostly due to physiological dysregulation caused by the fact that behavioural rhythms, such as sleep-wake and eating suddenly become out of phase with physiological rhythms, and physiological rhythms themselves desynchronise as some adapt faster to the transition than others (Arendt, 1998). Depending on the individual, adaptation to an eight-hour phase change can take between 2 days and 2 weeks (Ehret & Scanlon, 1983). The fact that the period of the human pacemaker is longer than 24-hours means that phase delays are better tolerated and adapted to than phase advances and, as such, jet lag associated with westward journeys tends to be less severe and of shorter duration than eastward travel (Aschoff, Hoffman, Pohl & Wever, 1975; Binkley, 1992). Efforts to accelerate resynchronisation via the use of melatonin, bright light and preparing for the new time zone prior to departure have all been reported to help to alleviate the symptoms of jet lag (Arendt, 1998b; Armstrong, 1991; Binkley, 1992).

Shift-Work Related Syndromes

Symptoms that are experienced as a result of shift-working are virtually identical to those reported by jet lagged travellers, a fact which is not surprising, given that their aetiology also involves forced desynchrony between an individual’s internal timekeeping mechanisms and the environmental cycle in which they operate. The major difference between the two syndromes is that jet lag is an acute phenomenon, that is experienced rarely or only intermittently by most sufferers, while shift-working entails
either regular phase alterations or constantly cycling at variance with the ambient solar and social rhythms. The chronic external desynchrony experienced by shift workers has been found to be related to higher rates of disturbances to sleep-wake and gastrointestinal systems and increased risk of cardiovascular disease and non-insulin dependent diabetes (Arendt, 1998a; Moore-Ede & Richardson, 1985). Other symptoms include fatigue that is unresponsive to sleep or rest, irritability, malaise and performance deficits (Reinberg, 1988). There is a high degree of inter-individual variability with respect to the capacity to tolerate shift-work (Moore Ede, Sulzman & Fuller, 1982) and, as a consequence, people who suffer the most from such schedules tend not to be shift-workers. Therefore, the rates of health problems in shift-workers are likely to understate the negative health consequences of chronic circadian dysregulation, for the population in general, and for the group of those more vulnerable individuals in particular.

_Circadian Disorders Due Mainly to Clock Malfunction_

Circadian Sleep Disorders

While jet lag and shift work related syndromes are the primary result of lifestyle or behaviourally induced disturbances to the circadian system, other disorders appear to arise from disturbances within the system itself. Circadian related sleep disturbances, such as delayed and advanced sleep-phase syndromes and non-24 hour sleep-wake syndrome appear to be related to intrinsic problems in period length or entrainment mechanisms (Moore-Ede et al., 1982). Even so, the nature of these disturbances tends to
put people at odds with the prevailing solar and social rhythms of their environments, and much of the discomfort and disability associated with them may arise from mechanisms similar to those operating with jet lag and shift-work. The major difference being, of course, that the external desynchrony is forced, rather than voluntary.

Circadian Disturbances Associated with Aging

Disturbed sleep patterns are common in older individuals, particularly the phenomenon of early waking (Dijk & Duffy, 1999). While it has been suggested that the need for sleep declines with age, overall sleep levels are no different with age, as older individuals who wake early usually make up for lost sleep by taking naps through the day (Czeisler et al., 1992). Evidence indicates that, rather than a need for less sleep, older adults experience problems with sleep duration and consolidation (Dijk & Duffy, 1999). The possibility that such sleep difficulties may be due to a degeneration of circadian functioning with age has been raised, but the evidence remains inconclusive. Sleep difficulties in older age do not appear to be associated with a shortening of the circadian period or reduced circadian drive for wakefulness (Dijk & Duffy, 1999). Also, while endocrine markers provide evidence of deterioration in circadian functioning in older age, these tend to occur somewhat later in life than the commencement of the decline in sleep function, especially that of slow-wave sleep (Van Cauter, Plat, Leproult & Copinschi, 1998). This chronology raises the possibility that age-related deterioration in sleep regulation may actually be responsible for alterations in circadian hormonal functioning, rather than vice versa. Another possible contribution to altered circadian
functioning in older age may be reduced exposure to regular and salient photic and non-photonic zeitgebers to which the system can reliably entrain itself. Decreased photic stimulation of the retina due both to lens discolouration and more time spent indoors, as well as reduced levels of physical activity, social contact and regularity of meal times might all contribute to poorer circadian organisation (Arendt, 1998; Van Cauter et al., 1998).

Circadian Dysregulation Associated with Mood Disorders

Lack of exposure to regular social zeitgebers has also been suggested to contribute to the aetiology of depression via disruption of the circadian system. Ehlers, Frank and Kupfer (1988) hypothesized that, apart from the clear psychological stress that is typically associated with major life events, specific events, such as the loss of a partner, may also lead to a sudden change in the presence or salience of social zeitgebers. They suggested that instability of social rhythms leads to instability of biological rhythms, particularly sleep. This state is then postulated to give rise to somatic symptomatology that, depending on individual psychological and physiological/genetic vulnerabilities, can persist and lead to major depression. The authors were careful to emphasise that they were not suggesting that this was the only pathway to major depression, but that it might apply in at least a subset of cases.

This theory was developed in the context of a body of research conducted over the past 40 years, that has linked mood disorders with altered sleep-wake (Wehr, 1988) and
endocrine rhythms (Deuschle et al., 1997; Weber et al., 2000; Wehr, 1988). However, while later studies indicated that social rhythms are disturbed in depressed patients (Brown et al., 1996; Szuba, Yager, Guze, Allen & Baxter 1992), the demonstration of a consistent biological rhythm disturbance in affective illness has proved elusive. A number of studies have reported specific disturbances of the circadian rhythms of various physiological parameters in mood disordered subjects. Abnormalities of phase (Fullerton, Wenzl, Lohrenz & Faha, 1968; Linkowski et al., 1985; Pflug, Erikson & Johnsson, 1976), waveform (Wehr, 1988) and amplitude (Candito et al., 1990; Schulz & Lund, 1985; Tsujimoto, Yamada, Shimoda, Hanada & Takahashi, 1990) have all been reported in patients suffering from affective disorders. However, the precise nature of abnormalities reported has varied. For instance, while some studies have reported phase advances (Fullerton et al., 1968, Linkowski et al., 1985), others have found delays (Avery et al., 1997; Daimon, Yamada, Tsujimoto & Takahashi, 1992) or no phase alterations (Daimon et al., 1992). Reduced amplitude of physiological rhythms is probably the most consistently reported circadian abnormality (Daimon et al., 1992; Tsujimoto et al., 1990; Wehr, 1988), although several studies have been unable to find any significant abnormalities at all (Monk et al., 1994; von Zerssen et al., 1985).

If rhythm disturbance is a characteristic of affective illness, perhaps it is most likely that it is manifested as general dysregulation, in which the stability of entrainment of rhythms to the external environment and to each other appears to be weakened (Daimon et al., 1992; Pflug et al., 1976; Teicher et al., 1997; Tsujimoto et al., 1990). Reduced
external and internal synchrony could explain reduced amplitude, in that inefficiencies caused by poor coupling of rhythms would result, in many cases, in the blunting of their expression. Many questions remain to be answered in this area, particularly with respect to the actiology of rhythm disturbances (pathological vs lifestyle), their role in the production and maintenance of symptoms, and their specificity to and within the affective illnesses.

Could Circadian Dysregulation Contribute to CFS?

So far, it has been established that circadian rhythmicity is a pervasive phenomenon, both across and within living organisms, including humans. The circadian timekeeping system serves the important purpose of maintaining temporal synchrony between an individual and the geophysical and social cycles of his or her environment, as well as the many behavioural and internal rhythms that occur every day. The genetic, neural and neurohormonal processes that underpin the capacity of humans and other organisms to maintain external and internal synchrony are complex, and not completely understood. It is clear, however, that the maintenance of temporal organisation is of central importance to the maintenance of proper functioning. Disruptions to the circadian system originate from both behavioural and physiological disturbances, and are known to lead to several well-defined states of ill-health, such as jet lag and shiftwork-related syndromes, as well as circadian sleep disorders. They also may contribute to some of
the decline in healthy functioning that is associated with advancing age, and to the generation or maintenance of some cases of affective illness.

It is noteworthy that many of the symptoms of CFS bear a striking resemblance to those associated with disrupted circadian functioning. Fatigue that is unresponsive to rest, general malaise, disrupted sleep, impairment of concentration, attention and performance and gastrointestinal disturbance are all symptoms that people with CFS share with many of those who suffer from jet lag and shift-work related syndromes. Certainly, the similarity was apparent enough to Thomas English, a medical doctor and CFS sufferer, to describe the illness as like suffering 'jet lag without end' (English, 1991, p. 265). On the basis of these similarities, it is reasonable to at least speculate that circadian disruption might also contribute to the symptoms of CFS. Although shared symptomatology does not always entail shared pathology, the fact that disorders of circadian timing often result in such complaints demonstrates that circadian dysregulation is at least capable of producing many of the core symptoms of CFS.

There are a number of other factors that are consistent with the involvement of circadian dysregulation in CFS. Firstly, and with respect to aetiology, the loss of social zeitgebers hypothesis, forwarded by Ehlers et al. (1988) as a possible aetiological factor in the onset of major depression, is probably even more attractive as a possible explanation for the onset of CFS. As has been mentioned in other sections of this review, the onset of CFS often follows the occurrence of major stressful life events, infections, or periods in
which the individual may have been ‘overdoing it’. All of these situations could entail a
loss of, or reduction in, an individual’s exposure to salient social/behavioural rhythms.
For instance, the immune response to infectious illness encourages (if not requires)
sufferers to withdraw from their usual social pattern to seek rest and quiet.
Convalescence typically entails disturbances to circadian patterns of sleep, activity,
cating and social interaction. Depending on the nature of the illness, and the ability of
the host to overcome it, these circadian disturbances can occur chronically or
intermittently over a long period. Moldofsky (1993; 1995) has also pointed out the
intimate link that exists between sleep-wake and immune systems, and that the presence
of infective agents directly produces alterations in sleep-structure. Similarly, a common
result of major stressful life events, such as the loss of a partner, changes in employment
status, the birth of a child and physical or emotional trauma, could be the loss of regular
social cues, and sleep may also be directly disturbed by stress itself. ‘Overdoing it’ at
work or socially could also often entail disturbances to usual sleep-activity and eating
patterns, the effects of which are likely to become more pernicious as the unhealthy
behaviour pattern continues.

The loss of regular social cues would be made even more significant by the likelihood
that exposure to a salient and regular light-dark cycle is also often reduced as a result of
these kinds of events. Savides, Messen, Senger and Kripke (1986) reported that, even in
healthy individuals, natural exposure to light of sufficient intensity and duration to exert
an entraining effect was uncommon. Presumably, under such circumstances, one’s
clock depends upon non-photic input in the form of regular sleep-activity, eating and social patterns in order to maintain external and internal synchrony. In the situations noted above, of illness, major stress, or of overextending one's self, light exposure is likely to be even more reduced or irregular, and the clock cannot fall back to relying on regular non-photic cues. Irregular patterns of rest-activity have been demonstrated to result in the loss of entrainment to the 24-hour day (Minors, Nicholson, Spencer, Stone & Waterhouse, 1986). Under such conditions, the natural tendency is for rhythms to free-run, and it is likely that chronically irregular social patterns would also severely undermine internal synchrony as the system is continually confounded by inconsistent cues.

It has also been demonstrated that social and/or physical stress produces significant disturbances to the circadian organisation of physiology and behaviour. Tornatzky and Miczek (1992) showed that intermittent social stress, over five days, resulted in a significant blunting of heart rate and core temperature rhythms in rats that lasted for at least 10 days. Opstad (1994) monitored circadian patterns of hormone secretion and mental performance in military cadets who underwent a five-day training course in which continuous heavy physical activity was undertaken while sleep and food intake was severely curtailed. The researcher reported that circadian rhythms of a number of hormones (e.g. cortisol, dihydrocpiandrosterone, progesterone, testosterone and thyroid stimulating hormone) were extinguished during the experiment and took several days of rest to reestablish. Mean levels of cognitive performance declined throughout the
experiment and, while the amplitude of the circadian rhythm (of cognitive performance) actually increased, this was a function of there being times of extremely low performance levels interspersed with times of higher but still relatively poor performance. In another study, Monteleone, Fuschino, Nolfe and Maj (1992) showed that physical stress during the evening significantly interfered with the circadian expression of melatonin and cortisol. In what might be seen as the reverse of this, animal studies have shown that immobilisation during the normal active period results in significant phase shifts of the biological clock (Van Reeth, Hinch, Tecco & Turek, 1991). This last point may have implications with respect to the possible occurrence of circadian dysregulation due to major life events or illnesses that render people inactive for a long period of time.

An aetiological role of circadian dysregulation in the onset and maintenance of CFS could also provide a mechanism for suggested inter-individual differences in vulnerability to the disorder (Demitrack, 1996). It could also partially explain the observation that women appear to be more at risk of prolonged fatigue than men (Kroenke et al., 1988; Lawrie & Pelosi, 1995). Studies in humans demonstrate unequivocally that genetic factors regulate circadian rhythmicity (Linkowski, 1994; Linkowski et al., 1993), including their sensitivity to disruption by external factors (Ashkonazi, Reinberg, Bicakova & Ticher, 1993). Presumably, genetic factors are, at least in part, responsible for the demonstrated inter-individual differences in the ability to tolerate shift-work, and may bestow a level of immunity/vulnerability to the onset and
or maintenance of circadian dysregulation. Earlier work has shown that sex differences exist in the periodicities of sleep-wake relative to those of core temperature, and that the influence of rhythm disorder is significantly greater in women than in men (Wever, 1986).

Moldofsky (1993, 1995) was the first to suggest that a chronobiological disturbance may be the central pathology underlying both CFS and fibromyalgia. Moldofsky (1995) assembled a comprehensive body of evidence that suggested that chronobiological disturbance could contribute significantly to non-restorative sleep, pain and disturbances of cognitive functioning and affect in CFS and fibromyalgia, through a complex interaction between the sleep-wake, immune, neuroendocrine and thermoregulatory systems. Moldofsky (1995) posited that a fundamental disturbance to the regulation of sleep-wake results in a pattern of dysregulation in these other systems, that gives rise to much of the core symptomatology of the two syndromes. In particular, he discusses the possible role of the cytokine interleukin-1 (IL-1) due to its central importance in the coordination of neuroendocrine and immune parameters in the regulation of the sleep-wake cycle, and its impact on various aspects of functioning that are relevant in CFS and fibromyalgia.

On the basis of the evidence presented above, it is suggested that examination of the circadian system in CFS sufferers is warranted. Firstly, dysregulation of the circadian system is known to be capable of producing complaints that are virtually identical to
those that make up the core symptomatology of CFS. Secondly, common events that appear to be aetiologically significant in CFS are likely result in circumstances in which the maintenance of external and internal circadian synchrony is difficult. Also factors such as stress and infection may have a direct impact on circadian integrity. Thirdly, evidence of genetic and sex differences in the vulnerability of the circadian system to dysregulation could explain why some individuals may be more prone to developing CFS than others, and why the disorder is apparently more prevalent in women.

Fourthly, Moldofsky’s (1995) review makes important links between circadian dysregulation and much of the phenomenology of CFS, particularly disturbances to sleep, immune, endocrine and affective functioning. The significance of these connections will be more fully discussed in later sections of this thesis.

A final aspect of the potential explanatory value of circadian dysregulation as a central feature of CFS, is that such dysregulation, along with previously discussed diagnostic issues and other methodological problems, could contribute to the remarkable heterogeneity of findings that is characteristic of research in the area. Many studies of physiological and psychological functioning in CFS take little or no account of the inherent circadian variation of the parameters under consideration. This is by no means a idiosyncratic failing of CFS research, however, it is likely to be even more problematic in populations where significant disturbances to sleep-wake and other circadian aspects of functioning occur. Most of the physiological parameters studied in CFS show marked circadian variation, as do many of the cognitive and psychological variables
investigated. The usual procedure for controlling for circadian variability, testing
subjects at the same time of day, is not reliable if there are differences between groups in
circadian functioning. When such differences exist and are systematic (e.g., a systematic
phase delay or phase advance in CFS patients relative to the comparison group), they are
likely to bias results. On the other hand, if the systematic difference was general
circadian dysregulation, the result might simply be increased error variance, and a
subsequent reduction in the power of experimental protocols to detect differences.

Empirical Studies of Circadian Rhythmicity in CFS

So far, the few research studies of circadian functioning in CFS patients display the
same bewildering heterogeneity of findings that characterises research into other aspects
of CFS. The factors underlying the inconsistency of results are largely the same as for
other areas, although some of the methodological issues are idiosyncratic to circadian
research. The most significant of these is the way in which controls are implemented to
account for exogenous factors that obscure or mask the endogenously driven component
of the rhythm being studied. Some studies have employed constant routines, in which
sleep is forgone and food intake is regulated, to control for the effects of sleep-activity
and caloric intake, while others purify the data post-hoc, by applying validated
algorithms to adjust raw values appropriately. Several studies have ignored these
important techniques and have employed only the most basic environmental controls for
ambient temperature and lighting. The validity of data collected under these conditions is highly questionable.

The first study of circadian functioning in patients with chronic, unexplained fatigue was carried out by a French group (Camus et al., 1992). Camus et al. (1992) monitored 24-hour core temperature variation in 45 patients with unexplained fever and chronic fatigue of at least 3 months duration. The investigators compared these data with those obtained from a further 40 patients hospitalised with fever of known origin and 16 healthy volunteers. Groups were not matched in terms of sex or age, although statistically adjusting for these suggested they had no impact. No apparent controls were implemented for stage of menstrual cycle.

Core temperature was monitored for 24-hours, in a single hospital room with constant ambient temperature. The investigators give no information with respect to controls for other salient variables, such as light exposure, sleeping and caloric intake. It is therefore assumed that the experiment was not conducted using a constant routine protocol. There was also no attempt to unmask, or purify the data in order to more clearly examine the endogenously driven component of temperature variation although, to be fair, purification techniques were only just appearing in the literature at that time. Fourier series were applied to summarise the temperature rhythms in terms of phase, temperature minimum, maximum, and amplitude. The investigators reported that the core temperature rhythms of the chronic fatigue-like unexplained fever group were of
significantly greater amplitude and phase advanced by two hours compared to those of both the explainable fever and control groups. Temperature maxima, minima and means of the unexplained fever group fell between those of healthy control and the explained fever groups (Camus et al., 1992). Using discriminant function analysis, the investigators were able to correctly classify the two fever groups with an efficiency of greater than 90% on the basis of the five temperature parameters.

Although the authors suggested that their study population was representative of CFS sufferers diagnosed using the 1988 CDC criteria (Holmes et al., 1988), this is apparently based on the absence of significant laboratory findings alone. Even if other appropriate psychiatric and other screening procedures had been carried out, the three month criteria for symptom presence is insufficient to meet the 6 months required by the CDC (Fukuda et al., 1994; Holmes et al., 1988). Also, while the presence of fever was a part of the CDC symptom criteria in 1988, it is not a particularly common feature in the presentation of sufferers, and was dropped in the 1994 revision (Fukuda et al., 1994). This raises further questions about the representativeness of the study population of CFS sufferers in general.

Two other studies have monitored circadian patterns of core body temperature in CFS patients, neither of which support the findings of Camus et al. (1992). The most recent of these was carried out by Hamilos et al. (1998), and compared 24-hour core temperature and plasma cortisol variation in CFS patients with that of age- and sex-
matched healthy controls, allergy sufferers, and patients with major depression. The investigators continuously monitored participants’ core temperature over a 24 hour period via ingestible radio transmitter thermometers. The investigators found no differences between any of the groups in terms of mesor and phase of the temperature rhythm, although amplitude was significantly reduced in the CFS group. They also noted that the goodness of fit of the cosine function, using a single harmonic analysis tended to be poorer in the CFS group. Four-hourly plasma cortisol sampling failed to detect any differences between groups. Given the small number of participants involved (seven in each group), and that the investigators employed neither constant routine nor purification techniques to control for exogenous influences on the core temperature rhythm, the lack of significant findings is not conclusive.

In the first study designed to systematically investigate whether CFS is associated with disturbances to circadian functioning, Williams et al. (1996) continuously monitored rectal temperature for 24 hours in 20 CFS patients and 18 age-matched healthy controls during their normal daily routines. The CFS group was also monitored for a further 24 hours during an elective hospital admission. Half-hourly plasma samples were collected from both groups under controlled conditions between 18:00 and 24:00 in order to obtain the dim light melatonin onset (DLMO), an accepted indicator of the phase of the melatonin secretion rhythm (Lewy, 1999). Raw temperature values were mathematically purified in order to estimate the endogenous component of the core temperature rhythm.
Core temperature rhythms did not differ between the groups on the parameters of phase, amplitude or mesor, and there were also no between-group differences with respect to DLMO. Interestingly, however, while the timing of DLMO and temperature acrophase showed the expected significant, positive correlation in healthy participants, there was no relationship between the two rhythms in the CFS group. The authors interpreted this finding as evidence of internal circadian desynchrony in CFS, and theorised that the dissociation between temperature and melatonin rhythms may be indicative of general temporal dysregulation. The authors were unable to conclude whether the disturbance was related to underlying pathology or lifestyle factors.

Interestingly, some of the same investigators (Leese et al., 1996) almost simultaneously published another study that suggested that disruptions to sleep and social routines of healthy participants produced similar disturbances of HPA axis functioning to those which had been reported as occurring in CFS patients (Demitrack et al., 1991). Leese et al. (1996) studied the HPA axis functioning of 10 nurses on shift rotation. The investigation was carried out using a repeated measures design, with testing occurring twice, once after five consecutive day-shifts and once after five consecutive night shifts. Relative to day-shift data, tests conducted during the night-shift phase showed significantly higher basal ACTH concentrations and, while these levels remained higher following CRH administration, the overall response from baseline was blunted. Conversely, baseline cortisol levels were lower during the night-shift phase, although
cortisol responses following CRH administration were greater relative to baseline at night. This suggested increased sensitivity of the glucocorticoid response to CRH induced ACTH increases during night-shift. Importantly, the authors argued that these results could not merely be explained by a global phase shift of circadian timing, as there were no indications that such changes had occurred. They also cited other work that has indicated that shift-work leads to decreases in the amplitude of cortisol secretory rhythms without altering phase (Touitou et al., 1990).

Given the small sample size and nature of the study population, these findings are of uncertain generalisability. Although sleep disturbances are common in CFS, few patients would be exposed to the inverted sleep-wake schedule associated with working a night shift. Nevertheless, they provide important evidence that the HPA axis dysfunction that has been repeatedly associated with CFS could be the result of dissociation of sleep-wake and SCN rhythms. This, of course, does not undermine the potential importance of HPA axis dysfunction in promoting the symptoms of CFS. However, it does offer a potential mechanism for its presence and, subsequently, potential avenues for its treatment.

Two recent studies have attempted to investigate the diurnal rhythm of cortisol secretion in CFS patients. One of these sampled CFS patients and controls at 8am and again at 8pm (MacHale et al., 1998). Morning cortisol levels were non-significantly lower in the CFS group, while evening levels were non-significantly higher. ACTH levels were non-
significantly higher at both times. The difference between morning and evening cortisol levels was significantly reduced in the CFS group and, interestingly, the magnitude of the difference correlated with functional improvement over the previous year and with social functioning. Evening levels of cortisol also correlated with measures of general health and physical functioning. The authors concluded that adrenocortical functioning was related to disability in CFS, although they were unable to draw conclusions about the causal nature of the relationship.

It is tempting to suggest that reduced variation between the evening and morning sample is evidence of reduced amplitude of the circadian rhythm of cortisol secretion. However, the cortisol rhythm may simply have been phase delayed in the CFS group, and the lower morning levels and higher evening levels may have been due to the fact that sampling occurred at different circadian times for each group. In that case, the correlations between disability and cortisol levels may be an artifact of a correlation between disability and the magnitude of the phase delay. More disabled individuals might be more phase delayed because they find it more difficult to rise earlier in the morning after a non-restorative sleep period.

Another study examined cortisol secretion over 16 hours in 10 healthy and 10 CFS participants (Wood, Wessely, Papadopoulos, Poon & Checkley, 1998). In contrast to the study described above, and to other studies suggesting that CFS patients demonstrate hypocortisolacemia, no significant differences were found in the cortisol profiles of the
two groups. In fact, cortisol levels over the sampling period were slightly higher in the CFS group. Again, however, these results may have been due to a slight phase delay in the cortisol rhythm, and visual inspection of the profiles suggests this is possible. Because neither study sampled across at least one entire 24-hour period, conclusions about differences in the circadian profiles of the groups cannot be drawn.

In the only other study of circadian functioning in CFS patients known to the writer, a Dutch group looked at rhythms of heart rate and blood pressure in 18 CFS sufferers and 12 age-matched normotensive controls (van de Luit, van der Meulen, Clephas & Zwinderman, 1998). Although the phase of the rhythms of heart rate, and diastolic and systolic pressure were similar, amplitudes for all three variables were substantially and significantly greater in the CFS group. The authors were unable to assess whether such patterns reflected cause or effect of the syndrome, and they did not make any suggestions as to the mechanism(s) that might have produced such a difference between groups.

**Proposal for the Systematic Study of Circadian**

**Timing in CFS**

Of the five studies of CFS patients reviewed above, only three monitored circadian variability over at least a 24-hour period. (Camus et al., 1992; van da Luit et al., 1998;
Williams et al., 1996). All three of these studies found significant differences between circadian profiles of healthy controls and CFS patients. Of the other two studies, one was suggestive of circadian abnormalities (MacHale et al., 1998) while the other found no difference (Woods et al., 1998). Each study monitored different parameters under different conditions with different subgroups of patients and, as such, it is difficult to draw firm conclusions. Their results do, however, lend some support to the hypothesis that circadian dysregulation occurs in CFS, and suggest further investigation is needed. The findings of Leese et al. (1996) in shift-workers are particularly intriguing, as they indicated that the HPA axis disturbances that are currently subject to intense investigation in CFS, could be secondary to a circadian disturbance that is characterized primarily by external desynchrony. To date, however, circadian profiles of sleep-activity have not been assessed in CFS, and so would be a reasonable starting point for the systematic investigation of the integrity of the circadian timekeeping system in CFS sufferers.

The purpose of such a study would be to investigate whether sleep-activity patterns of CFS sufferers are disturbed, in order to assess whether the kind of mechanism suggested by Leese et al. (1996) in their study of shift-workers could be apply in CFS. It would also be appropriate to investigate the relationship between the sleep-wake cycle and the rhythm of the SCN, in order to determine whether a degree of internal desynchrony exists in CFS. It has been shown that various important physiological and mental processes can be undermined when the sleep-activity cycle is not properly coupled with
the endogenous pace-maker (Van Cauter, 1990), and many of these have relevance to CFS. Dijk and Czeisler (1994) showed entrainment of the sleep-wake cycle and circadian pacemaker promotes the consolidation of sleep and wakefulness, as well as healthy sleep structure. Dissociation between the two rhythms has been shown to negatively affect cognitive functioning (Dijk, Duffy & Czeisler, 1992), alertness (Czeisler, Dijk & Duffy, 1994) and mood (Boivin et al., 1997) in otherwise healthy individuals. Van Cauter (1990) reviewed evidence from a number of studies indicating that the expression of every pituitary and pituitary dependent hormone (including those of the HPA axis) was influenced by both the signal emanating from the SCN and the cycle of sleep-wake. Patterns of glucose regulation and insulin secretion also appear to be dependent on sleep-wake/SCN synchrony (Scheen & Van Cauter, 1998; Simon, 1998).

Finally, even if such investigations provide clear evidence for the presence of circadian disturbance in CFS, their clinical significance will remain unclear. Prospective studies would therefore be required to assess the impact of circadian disturbances on the symptomatology of CFS. These would necessarily entail the testing of interventions designed to restore circadian integrity, and pre-post comparison of symptom severity and disability.

The general aim of the following series of studies is, therefore, to conduct a systematic and well-controlled investigation into the integrity of the circadian time-keeping system
in people who meet the CDC criteria for the diagnosis of CFS (Fukuda et al., 1994). While this investigation will initially focus on whether the behavioural and physiological circadian functioning of people with CFS is altered compared to appropriately matched healthy individuals, an attempt will also be made to assess the relationship between any alterations detected and the symptoms of the illness. In order to fulfil these aims, the studies will seek to answer four specific questions about circadian functioning and CFS. These are:

1. Is the circadian expression of the sleep-activity patterns of CFS sufferers altered in comparison to healthy controls?

2. Is the circadian expression of the physiology of CFS sufferers altered in comparison to healthy controls?

3. Is the relationship between behavioural and physiological rhythms altered in CFS sufferers in comparison to healthy controls?

4. If any alterations in circadian functioning are found to exist in CFS patients, are they related to aspects of symptomatology, and what is the nature of that relationship?
The first two of these questions deal primarily with the issue of the external synchrony of behavioural and physiological rhythms and, as such, the focus will be on whether the phase positioning of these rhythms relative to the ambient light-dark cycle is altered compared to controls. Other aspects of rhythm expression, such as amplitude, mesor and goodness of fit to a 24-hour period will also be compared. The general hypothesis is that CFS participants, compared to controls, will demonstrate reduced salience of their behavioural and physiological rhythms, and evidence of poorer entrainment to the external light-dark cycle. The third question deals directly with the issue of internal synchrony, assessed as the strength of relationship between sleep-wake and the endogenous cycle of the SCN. It is hypothesised that CFS patients will demonstrate weaker entrainment of the sleep-wake cycle with the endogenous rhythm of the SCN. As the output of the SCN cannot be measured directly, the endogenously driven component of the core temperature rhythm will be used as an indicator of SCN timing. The final question deals directly with the issue of the clinical significance of circadian abnormalities, should they be detected. The general hypothesis is that any evidence of reduced salience of circadian functioning, or lack of external or internal synchrony will be related to at least some aspects of symptomatology.

A hypothetico-deductive process will be followed, in which successive experiments will be designed on the basis of the results of previous findings. The logical starting point is
an examination of circadian patterns of sleep-activity of CFS patients, and this is the subject of the first experimental chapter, which now follows.
CHAPTER 5

STUDY 1: CIRCADIAN SLEEP-ACTIVITY PATTERNS IN CFS SUFFERERS AND HEALTHY CONTROLS
**Introduction**

Although several studies have investigated sleep in CFS patients, these have mainly focused on the presence of identifiable sleep disorders or polysomnographic changes (Buchwald et al., 1994; Krupp et al., 1993; Manu et al., 1994). One study that specifically investigated the sleep behaviour of CFS patients compared to healthy controls, found that CFS patients spent significantly longer in bed, slept less efficiently, and spent more time awake after sleep onset (Sharpley et al., 1997). No studies of CFS have examined circadian patterns of sleep-activity, or relationships between circadian functioning and sleep disturbance.

Such a study is warranted for several reasons. Firstly, the study of circadian sleep-activity patterns is the logical first step in the examination of circadian integrity in CFS. Secondly, the findings of Leese et al. (1996) suggest that the dysregulated HPA axis function that has been reported in CFS patients (Demitrack et al., 1991) also occurs in shift-workers following a series of night shifts. It would, therefore, be useful to examine the circadian profiles of sleep-activity in people with CFS to investigate for the presence of rhythm disturbances that may underlie HPA axis abnormalities. Thirdly, Investigation of circadian sleep-activity patterns may provide clues as to whether the previously reported disturbances to sleep-efficiency (Sharpley et al., 1997) are related to
dysregulated circadian functioning. It has been suggested that the primary role of the
circadian time-keeping system in sleep-regulation is in the consolidation of the nocturnal
sleep period in order to maintain sleep-efficiency (Dijk & Czeisler, 1995). Finally,
systematic differences, particularly with respect to phase, in circadian sleep-activity
patterns may exist between people with CFS and healthy individuals. This would be a
significant methodological issue in research that has investigated for abnormalities on
parameters that vary in their expression across the 24-hour day. Reports of altered
hormonal or immunological parameters could be an artefact of altered circadian timing.
This would apply to virtually all physiological, and some of the psychological and
behavioural parameters that have been investigated in CFS research to date.

The following study was undertaken in order to address these issues. The first aim was
to investigate sleep-activity rhythms of a group of CFS patients compared to those of age
and sex matched controls. The second aim was to examine patterns of sleep behaviour,
with respect to sleep timing, duration, consolidation and variability. The third aim was
to examine whether circadian abnormalities are related to abnormalities of sleep, and
also whether either of these are significant contributors to deficits in physical and
emotional well-being.
Method

Participants

Thirty-two people who satisfied the Centers for Disease Control (CDC) criteria for the diagnosis of CFS (Fukuda et al., 1994) were drawn from a larger group of patients who had either been referred to the University CFS Clinic by their physician or had self-referred. Regardless of the method of referral, acceptance into the study required verification that the appropriate pathological screening tests recommended by the CDC had been carried out within the 6 months immediately prior to referral. The minimum battery of tests required by the CDC entails: complete blood count with leukocyte differential; erythrocyte sedimentation rate; serum levels of alanine aminotransferase, total protein, albumin, globulin, alkaline phosphatase, calcium, phosphorus, glucose, blood urea nitrogen, electrolytes, and creatinine; determination of thyroid-stimulating hormone; and urinalysis (Fukuda, 1994). Patients’ own physicians were asked to provide such verification. Where tests had been carried out with abnormal findings, verification from the physician was sought to establish whether the cause of the abnormality had been detected and treated successfully. Participants whose pathological screening met the CDC criteria then underwent a structured clinical interview (Appendix A), during which there was a comprehensive assessment of symptoms and illness,
general medical and psychiatric histories. This interview was conducted by a clinical psychologist experienced in the assessment of CFS patients, and generally took between 1.5 and 2.5 hours. Psychiatric screening was carried out through a combination of mental status examination, history and psychometric assessment via the Minnesota Multiphasic Personality Inventory-2 (MMPI-2: Butcher, Dahlstrom, Graham & Tellingen, 1989). Those patients who qualified for current or past psychiatric diagnoses that preclude the diagnosis of CFS, (e.g. any of the schizophrenias, bipolar disorder, anorexia nervosa: Fukuda et al., 1994) were excluded from participation in the study.

Thirty-two healthy controls were recruited in order to match the CFS group with respect to sex, age and, as far as possible, number of hours of work or study per week. Healthy participants were recruited by word of mouth and advertisements placed around the university, and were paid for their participation. In order to control for the amount of externally imposed daily routine, attempt was made to match groups on the basis of number of hours spent per week in paid work. Both CFS and control groups were made up of 8 men and 24 women. Healthy controls ranged in age from 20-68, with a mean of 37.44 (SD=12.93). Age range for CFS participants was 18-67 years, with a mean of 37.81 (SD=13.40). Controls worked an average of 14.50 hours per week (SD=13.8) while CFS participants averaged 9.23 hours (SD=12.3).
**Materials and Procedure**

The study protocol was approved by the university ethics committee. Sleep-activity patterns were assessed via participants filling out a sleep-activity log-book for 14 days. An example of the log-book and instructions for its completion are provided in Appendix B. The log-books required participants to categorise their level of activity for every fifteen minute period of the day. The four categories of activity were: Sleep (time actually spent asleep), Rest (time spent resting, but not sleeping), Sedentary Activity (time spent doing things while sitting or lying down), Heavier Activity (time spent doing things involving significant physical movement). The log also allowed participants to record their eating times, although this was not examined in the present study.

Information from the logs was entered into a statistical package as frequencies for each 15 minute period for each variable (boxes were coded as ‘1’ if marked, and ‘0’ if unmarked). The activity profile was generated by the algorithm: (Heavy activity x3) + (Sedentary Activity) - (Rest) - (Sleep x 3). The equation was applied to each 15-minute window of the log, and the resulting figures provided a sleep-activity profile for each person for the 14 days on a 7 point ordinal scale (-3 to +3).

In order to assess the accuracy of the data obtained by the log, half of the participants from each group also wore wrist activity monitors (Gachwiler Electronic, Switzerland) for between 4 and 7 of the 14 days of self-monitoring. The monitors contain movement
detectors (accelerometers) and record the frequency of movements made by a participant during specified intervals over any give time period. In this case, 15-minute intervals were specified, in order to match the units of time recorded in the log-book. Half of the participants who wore the monitors did so during the first week of self-monitoring, and half during the second. The study was conducted during late winter and spring (southern hemisphere) of 1998. An equal number of CFS participants and controls always underwent the procedure concurrently so as to control for seasonal or weather factors.

Both log-book and wrist monitor data were analyzed via non-linear least squares regression using a software package specifically developed for the analysis of biological rhythm data (Cosifit, Circesoft, Waltham, MA, USA). This analysis finds the cosine function that best fits each individual’s data and provides the summary statistics of acrophase, amplitude, mesor and frequency, as well as goodness of fit to the cosine function (Tiecher & Barber, 1990). The parameter ‘acrophase’ represents the timing of the daily peak in the sleep-activity rhythm, and provides an indication of the phase position of the rhythm relative to the ambient environmental cycle. The parameter ‘amplitude’ provides an indication of the salience of the rhythm, in that it is a measure of the average difference between the day-time rise in activity and the night-time fall. ‘Mesor’ is, simply, the mean activity level, while frequency is the number of cycles per 24-hour period.
Results

Prior to analysis, all data were screened for normality, linearity and homoscedasticity. Appropriate adjustments were made, where necessary, according to procedures outlined by Tabachnik and Fidell (1996).

Sleep-Activity Log-book Validation

The results of the log-book and activity meter methods were compared to obtain an indication of the validity of the data collected through the self-monitoring method. This procedure was also aimed at assessing whether the validity of the log-data was similar for the CFS and control groups. Table 5.1 presents the correlations between rhythm parameters calculated for data collected concurrently via the sleep-activity log-books and wrist activity meters in the 32 CFS and healthy control participants who used both methods for at least 4 days during the 2-week monitoring period. Pearson’s r coefficients were calculated for each rhythm parameter for the entire validation study sample, and separately for each group.

The coefficients presented in Table 5.1 indicate that all four rhythm parameters obtained from the log-book correlated significantly with those obtained via wrist activity monitoring. Of these, mesor and amplitude were the weakest correlations, and this can reasonably be attributed to several important differences in the nature of the data.
collected by the different methods. Wrist-activity monitoring does not differentiate between sleep and waking inactivity, nor can it distinguish whether periods of high wrist movement frequencies represent substantial movement of the whole body (eg walking) or just of the arm or wrist (eg typing, knitting, or even being a passenger in a vehicle on a bumpy road).

Table 5.1.

Pearson’s correlation coefficients between wrist-monitor and log-book determined sleep-activity parameters for healthy and CFS participants.

<table>
<thead>
<tr>
<th>Rhythm Parameter</th>
<th>Entire</th>
<th>Healthy</th>
<th>CFS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sample</td>
<td>n=16</td>
<td>n=16</td>
</tr>
<tr>
<td>Phase</td>
<td>.85 ***</td>
<td>.83 ***</td>
<td>.83 ***</td>
</tr>
<tr>
<td>Mesor</td>
<td>.35 *</td>
<td>.27</td>
<td>.57 *</td>
</tr>
<tr>
<td>Amplitude</td>
<td>.57 **</td>
<td>.57 *</td>
<td>.60 *</td>
</tr>
<tr>
<td>Frequency</td>
<td>.73 ***</td>
<td>.83 ***</td>
<td>.61 *</td>
</tr>
</tbody>
</table>

*p<.05; **p<.01; ***p<.001.

Importantly, coefficients calculated for each group on each of the parameters indicate that the relationships between log-book and activity monitor data were similar for CFS and controls. Although the control group’s correlation for activity mesor appears to be poorer than that of the CFS group, statistical comparison of the coefficients using Fisher’s Z found the difference to be non-significant (Z = 0.97, p > .05). However, the
differences outlined above between the nature of the data collected via the different methods may be more salient with healthy individuals, given that they are likely to engage in substantial physical activity more often than people with CFS. Nevertheless, the results of the comparison between log-book and wrist monitor methods offers no reason to doubt the validity of the log-book data as an indicator of circadian patterns of sleep-wake in either CFS or control groups.

Circadian Sleep-Activity Rhythms

Table 5.2 displays the means and standard deviations for the sleep-activity parameters calculated from the 14-day log-book self-monitoring procedure. The five parameters were assessed as dependent variables (DV) in a MANOVA procedure, with group as the independent variable (IV). As with all other MANOVAs reported in this thesis, Pillai's criterion was used. A significant overall between group difference was found using this procedure $F(5,58)=8.00$, $p<.001$. Univariate ANOVAs were then used to investigate the DVs individually, and this procedure detected significant between group differences for mesor $F(1,62)=33.10$, $p<.001$, amplitude $F(1,62)=14.42$, $p<.001$, and phase $F(1,62)=6.40$, $p<.05$. Groups did not differ in terms of frequency $F(1,62)=0.53$, $p>.05$ nor goodness of fit of the cosine function $F(1,62)=2.54$, $p>.05$. 
Table 5.2.

Means and standard deviations for sleep-activity rhythm parameters in CFS and healthy control groups

<table>
<thead>
<tr>
<th>GROUP</th>
<th>Mesor</th>
<th>Amplitude</th>
<th>Frequency</th>
<th>Phase</th>
<th>Fit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>M .20</td>
<td>2.64</td>
<td>1.00</td>
<td>15:27</td>
<td>.78</td>
</tr>
<tr>
<td></td>
<td>SD .26</td>
<td>.28</td>
<td>0.05</td>
<td>0:57</td>
<td>0.05</td>
</tr>
<tr>
<td>CFS</td>
<td>M -.24***</td>
<td>2.37***</td>
<td>1.00</td>
<td>16:11*</td>
<td>.76</td>
</tr>
<tr>
<td></td>
<td>SD .35</td>
<td>.28</td>
<td>0.05</td>
<td>1.20</td>
<td>0.06</td>
</tr>
</tbody>
</table>

p<.05; **p<.01; ***p<.001.

A significantly lower sleep-activity mesor indicated that the CFS participants were, on average, less active than controls over the 14-day period. Rhythm amplitude was also significantly lower, indicating that the difference between day and night, in terms of activity levels, was smaller for the CFS group. The figures for mesor and amplitude, presented in Table 5.2 are derived from the 7-point scale of the sleep-activity log-books, which weights sleep as −3, resting as −1, sedentary activity as 1 and heavy activity as 3. Given that this is an ordinal scale, it is not possible to calculate meaningful estimates of the actual magnitude of differences between groups. The CFS group was also significantly phase delayed, by 44 minutes on average, compared to controls. Figure 5.1 depicts the averaged diurnal activity patterns of each group across the two-week period.
**Figure 5.1.** Sleep-activity patterns of CFS and Healthy groups, averaged across the 14-day self monitoring period. The scale of measurement is ordinal, with −3 representing sleep; −1 = rest; 1 = sedentary activity; and 3 = heavy activity.

**Sleep Timing**

Table 5.3 presents the means and standard deviations for the five variables pertaining to the timing of the nocturnal sleep period. The overall positioning of the nocturnal sleep phase was operationalised as sleep midpoint, which was calculated by determining the midpoint between median sleep-onset and waking over the 14 days for each participant. Times of retiring, sleep-onset, final waking and rising were also averaged for each
participant over the two-week period. These variables were tested together, as
dependent measures, in a MANOVA as dependent measures, with group as the
independent variable. A significant overall group difference was detected $F(5,58)=2.96,
p<.05$, with follow-up ANOVAs finding significant differences on sleep-midpoint
$F(1,62)=4.61$, $p<.05$, waking-time $F(1,62)=8.02$, $p<.01$, and rising time $F(1,62)=11.01$, $p<.01$. No differences were detected for times of retiring $F(1,62)=0.00$, $p>.05$ or sleep
onset $F(1,62)=1.24$, $p>.05$.

Table 5.3.

**Group means and standard deviations for sleep timing variables.**

<table>
<thead>
<tr>
<th></th>
<th>Sleep-midpoint</th>
<th>Retiring-time</th>
<th>Sleep-onset</th>
<th>Wake-time</th>
<th>Rising-time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>$M$ 3:37</td>
<td>-0.44*</td>
<td>-0.13</td>
<td>7.29</td>
<td>8.02</td>
</tr>
<tr>
<td></td>
<td>$SD$ 0:44</td>
<td>0:54</td>
<td>0:49</td>
<td>0:52</td>
<td>0:20</td>
</tr>
<tr>
<td>CFS</td>
<td>$M$ 4:20&quot;</td>
<td>-0.44*</td>
<td>0:10</td>
<td>8:31&quot;</td>
<td>9:15&quot;</td>
</tr>
<tr>
<td></td>
<td>$SD$ 1:22</td>
<td>1:14</td>
<td>1:18</td>
<td>1:36</td>
<td>0:34</td>
</tr>
</tbody>
</table>

* $p<.05$; ** $p<.01$; *** $p<.001$.
* Negatives indicate the value should be read as minutes before midnight.

These results indicate that, while CFS participants tended to retire and fall asleep at a
similar time of day to controls, their times of waking and rising were significantly
delayed, by 62 and 73 minutes respectively. Overall, the nocturnal sleep period of the
CFS group was phase delayed by 43 minutes; almost identical to the delay found for the
sleep-activity rhythm. Further analysis revealed no differences between groups with
respect to whether participants woke naturally, or by alarm or other external cue

t(62)=0.55, p>.05. CFS participants woke by natural means 77% of the time compared
to controls, who woke naturally on 74% of days.

Sleep-Timing Variability

As well as comparing groups on the actual timing of the sleep period, within group and
within subject variability was examined. Data presented in Table 5.4 are the within
group variances and mean within subject variances in sleep-timing parameters. Within
group variances indicate the amount of variability in the sleep timing parameters
between participants in the CFS and control groups. Higher variances indicate that
participants within a group are more variable relative to each other. The F-test applied to
determine the significance of differences between group variances was taken from
Howell (1982). The results below indicate that the CFS group was more significantly
variable with respect to the overall timing of the nocturnal sleep period, with sleep onset,
waking, and rising times all displaying more variability.

Within subject variances indicate the average inter-day stability in the respective sleep
timing parameters for participants in each group. Within subject variances were
obtained by calculating the variance on each parameter for each participant over the 14-
day self-monitoring procedure. Data presented in Table 5.4 are group means. Higher
variances in this case indicate that participants show less consistency in their sleep patterns from day to day. MANOVA found no significant differences between groups in the stability of timing across the five parameters $F(5,58)=2.21$, $p>.05$. Thus, CFS participants demonstrated no more inter-day variability than controls.

### Table 5.4.

**Between group comparisons of between subject variability (within group variances) and between day variability (average within subject variances) in sleep-timing parameters.** Data presented are variances expressed in units of hours.

<table>
<thead>
<tr>
<th></th>
<th>Sleep-midpoint</th>
<th>Retiring</th>
<th>Sleep-onset</th>
<th>Wake-time</th>
<th>Rising</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Within Group Variability</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy</td>
<td>.54</td>
<td>.81</td>
<td>.68</td>
<td>.76</td>
<td>.88</td>
</tr>
<tr>
<td>CFS</td>
<td>1.90</td>
<td>1.52</td>
<td>1.70</td>
<td>2.60</td>
<td>2.66</td>
</tr>
<tr>
<td>$E(31.31)$</td>
<td>3.50</td>
<td>1.87</td>
<td>2.50</td>
<td>3.42</td>
<td>3.02</td>
</tr>
<tr>
<td><strong>Within Subject Variability</strong></td>
<td>(Interday Stability)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Healthy</td>
<td>.84</td>
<td>20.02</td>
<td>34.00</td>
<td>1.07</td>
<td>1.67</td>
</tr>
<tr>
<td>CFS</td>
<td>.60</td>
<td>16.49</td>
<td>21.86</td>
<td>1.35</td>
<td>1.91</td>
</tr>
</tbody>
</table>

$p<.05$; $^{**}p<.01$; $^{***}p<.001$. 

Night-time Waking and Day-time Sleeping

Table 5.5 provides mean and standard deviations for variables measuring the frequency and duration of night-time wakings and day-time naps. Number of wakings represents the average frequency of wakings occurring between sleep-onset and the last waking prior to rising. Average total duration of time spent awake during this period is also presented. Similarly, number of naps represents the average frequency of sleep periods occurring outside of the nocturnal sleep period, and time spent napping represents the daily average in terms of nap duration. These variables were tested as dependent measures in MANOVA, with group as the IV. A significant overall effect was detected.

Table 5.5.

Night-time waking and day-time sleeping behaviour in CFS and healthy control groups.

<table>
<thead>
<tr>
<th></th>
<th>Number of wakings</th>
<th>Time spent awake during the sleep period</th>
<th>Number of naps</th>
<th>Time spent napping during the day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>M .72</td>
<td>0.18</td>
<td>0.05</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>SD .53</td>
<td>0.14</td>
<td>0.08</td>
<td>0.09</td>
</tr>
<tr>
<td>CFS</td>
<td>M 1.36 *</td>
<td>0.38 *</td>
<td>0.18 ***</td>
<td>0.13 ***</td>
</tr>
<tr>
<td></td>
<td>SD 1.30</td>
<td>0.33</td>
<td>0.16</td>
<td>0.13</td>
</tr>
</tbody>
</table>

* p < .05; ** p < .01; *** p < .001.
\[ F(4,59) = 5.99, p < .001. \] The CFS group woke almost twice as often as controls during the night \[ F(1,62) = 5.79, p < .05, \] and spent more than twice as long awake \[ F(1,62) = 7.14, p < .05. \] The CFS group also napped more than three times as often as controls \[ F(1,62) = 18.81, p < .001, \] and spent more than three times as long in day-time naps \[ F(1,62) = 14.33, p < .001. \]

*Total Sleep, Latency and Efficiency.*

A between group analysis was conducted on sleep-onset latency, sleep efficiency and overall amount of sleep, excluding and including naps. Sleep-onset latency was calculated for each participant as the average time between retiring and falling asleep. This measure was used because longer sleep-onset latencies can be indicative of a relative phase delay in the SCN rhythm, as has been demonstrated in sleep-onset insomniacs (Morris, Lack & Dawson, 1989). Sleep efficiency was calculated by dividing each participant’s total nocturnal sleep time by their total time in bed between initial sleep onset and final waking. These four variables, which are presented in Table 5.6, were again tested as DVs in MANOVA, which detected a significant overall effect \[ F(4,59) = 8.93, p < .001. \] Univariate ANOVAs found that the CFS group took significantly longer to get to sleep \[ F(1,62) = 12.68, p < .001, \] and had significantly poorer sleep efficiency \[ F(1,62) = 7.88, p < .01. \] Total time spent in sleep, however, did not differ significantly between groups, regardless of whether day-time naps were excluded \[ F(1,62) = 1.78, p > .05 \] or included \[ F(1,62) = 3.26, p > .05. \]
Table 5.6.

Group means and standard deviations for sleep-onset latency, efficiency, and total time spent in sleep excluding and including naps.

<table>
<thead>
<tr>
<th></th>
<th>Sleep-onset latency</th>
<th>Sleep efficiency</th>
<th>Total nocturnal sleep</th>
<th>Total sleep (including naps)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>M 0:31</td>
<td>0.96</td>
<td>7:23</td>
<td>7:27</td>
</tr>
<tr>
<td></td>
<td>SD 0:23</td>
<td>0.03</td>
<td>0:51</td>
<td>0:52</td>
</tr>
<tr>
<td>CFS</td>
<td>M 0:54 ***</td>
<td>0.92 ***</td>
<td>7:42</td>
<td>7:54</td>
</tr>
<tr>
<td></td>
<td>SD 0:31</td>
<td>0.07</td>
<td>1:00</td>
<td>1:04</td>
</tr>
</tbody>
</table>

*p < .05; **p < .01; ***p < .001.

Pearson’s bivariate correlation coefficients were calculated in order to determine whether increased sleep-onset latency in CFS participants was related to daytime napping, and also to determine whether later waking was related to poor sleep efficiency through the night. Contrary to what might be expected, increased napping behaviour was associated with shorter sleep-onset latencies $r(31) = 0.37, p < .05$. Later waking time was not significantly associated with reduced sleep efficiency $r(31) = -0.25, p > .05$.

**Physical and Emotional Well-being**

For each day of the log-book monitoring procedure, participants rated their physical and emotional well-being on a scale from 1 to 10 in the hour after waking and the hour
before bedtime. Paired t-tests indicated no differences between the ratings during the morning and those at night (p>.05) and, as such, morning and evening ratings were combined to provide single daily ratings. Group means for each of these are provided in Table 5.7. MANOVA, which incorporated these variables as dependent measures, found an overall significant group difference F(2,61)=35.78, p<.001. Univariate ANOVAs indicated that CFS participants scored significantly lower on both physical F(1,62)=73.30, p<.001 and emotional F(1,62)=22.68, p<.001 well being measures.

**Table 5.7.**

**Group means and standard deviations for daily physical and emotional well-being ratings.**

<table>
<thead>
<tr>
<th></th>
<th>Physical well-being</th>
<th>Emotional well-being</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>M 7.57</td>
<td>7.81</td>
</tr>
<tr>
<td></td>
<td>SD 1.08</td>
<td>1.11</td>
</tr>
<tr>
<td>CFS</td>
<td>M 4.30***</td>
<td>6.18***</td>
</tr>
<tr>
<td></td>
<td>SD 1.45</td>
<td>1.39</td>
</tr>
</tbody>
</table>

*p<.05; **p<.01; ***p<.001.

In order to assess whether differences detected on sleep-activity rhythm and sleep-onset latency and efficiency parameters were related to physical and emotional well-being in the CFS group, Pearson’s coefficients were calculated. These are presented below, in Table 5.8.
Table 5.8.

Correlations between sleep-onset latency, efficiency, sleep-activity rhythms parameters and measures of physical and emotional well-being for the CFS group only.

<table>
<thead>
<tr>
<th></th>
<th>Sleep-onset latency</th>
<th>Sleep efficiency</th>
<th>Sleep-activity mesor</th>
<th>Sleep-activity amplitude</th>
<th>Sleep-activity acrophase</th>
<th>Physical well-being</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep efficiency</td>
<td>- .33</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep-activity mesor</td>
<td>-.59 ***</td>
<td>-.03</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep-activity amplitude</td>
<td>-.43 *</td>
<td>.14</td>
<td>.40 *</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sleep-activity acrophase</td>
<td>.34</td>
<td>-.12</td>
<td>-.25</td>
<td>-.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical well-being</td>
<td>-.54 **</td>
<td>.00</td>
<td>.32</td>
<td>.44 *</td>
<td>-.23</td>
<td></td>
</tr>
<tr>
<td>Emotional well-being</td>
<td>.21</td>
<td>.02</td>
<td>.04</td>
<td>.16</td>
<td>.13</td>
<td>.56</td>
</tr>
</tbody>
</table>

*p<.05; **p<.01; ***p<.001.

Results presented in Table 5.8 show significant correlations between physical well-being and sleep-onset latency and the amplitude of the sleep-activity rhythm. Increased time taken to get to sleep at night was associated with poorer physical well-being. While
there was a modest but non-significant trend towards an association between sleep-latency and sleep-efficiency (p = .068), sleep efficiency was not correlated with well-being measures. Increased amplitude of the sleep-activity rhythm was associated with better physical well-being. Emotional well-being was not correlated with any of the sleep or rhythm parameters. Sleep-onset latency was correlated negatively with amplitude and mesor of the sleep-activity rhythm. Thus, longer latencies were more likely to occur in CFS patients with flatter, less active profiles. As would be expected, sleep-activity mesor was also correlated with amplitude.

Finally, because physical well-being was correlated with both sleep onset latency and the amplitude of the sleep-activity rhythm, the relationship between physical well-being and sleep-onset latency was tested with the effects of sleep-activity amplitude partialled out. The association between physical well-being and sleep-onset latency remained significant $r_{(20)} = -0.46$, $p < .05$. This indicates that sleep-onset latency was associated with physical well-being independently of the amplitude of the sleep-activity rhythm.
Discussion

Analysis of the 14 day log-book data indicated a number of important differences in circadian sleep-activity patterns exist in CFS sufferers compared to age and sex-matched healthy individuals. As expected, overall activity levels were reduced in the CFS group, as was the amplitude of the sleep-activity rhythm. The entire sleep-activity rhythm was phase delayed by approximately 45 minutes in the CFS group. The nocturnal sleep period was also phase delayed in the CFS group, although this was mainly due to later waking time, rather than to later retiring or sleep-onset time. While the CFS group were more heterogeneous with respect to the timing of the nocturnal sleep phase, there was no evidence that individual participants in the CFS group were less regular in their sleeping patterns than controls. With respect to disturbance to the normal sleep-wake rhythm, the CFS group woke more often and spent longer awake during the night. They also napped more often and for longer periods of time during the day. As a result of this, and the fact that they generally took longer to fall asleep at night, overall sleep efficiency was significantly reduced in the CFS group. Nevertheless, total sleep time was not significantly greater in CFS participants, even when time spent napping was included.

As expected, the CFS group scored significantly more poorly on measures of physical and emotional well-being. While emotional well-being was not related to any of the circadian sleep-activity or sleep quality variables, poorer physical well-being was associated with longer sleep-onset latencies and flatter sleep-activity profiles. Sleep
efficiency, a measure that is indicative of disturbed nocturnal sleep, was not related to well-being measures.

The findings with respect to alterations to sleep are virtually identical to those of another study employing sleep-diaries with CFS patients. Sharpely et al. (1997) also found that their group of non-depressed CFS patients spent longer in bed, slept less efficiently, spent more time awake after initial sleep onset but, overall, did not sleep longer than healthy patients. The authors suggested that, while they may be common in people with CFS, these sleep disturbances were unlikely to be major contributors to the symptomatology of the syndrome. The lack of any correlation between measures of sleep efficiency and well-being in the present study tends to support this view. However, regular disturbances to nocturnal sleep cannot be completely discounted as a maintaining factor in CFS, as chronic disturbances to sleep structure may have effects that build over time and are not acutely apparent. Research suggests that one of the primary roles of the circadian system in the regulation of sleep-wake is in the consolidation of nocturnal sleep to one continuous, efficient eight-hour (approximately) period and the consolidation of daytime wakefulness (Dijk & Czeisler, 1994; 1995). The findings that CFS patients went to bed at similar times and with similar, if not greater consistency compared to controls, suggests that poor sleep habits are, at least with respect to timing, not likely to be the source of their sleep disturbance. Further to this, while rising times were later in CFS patients, this was because of later waking times and
not due to CFS patients remaining in bed longer following waking than the healthy group.

The findings of reduced overall activity levels and flatter sleep-activity profiles were expected, given that by its nature, CFS is an illness that restricts physical activity. Reduced physical activity, and more frequent night-time wakings and day-time naps combined to reduce overall sleep-activity amplitude and, as a result, the salience of the sleep-activity rhythm. One possible, if not likely, consequence of this would be a reduction in the number and/or salience of non-photic cues available to assist the effective entrainment of the SCN to the ambient light-dark cycle. As has been discussed previously, the importance of non-photic cues is increased in the absence of exposure to a salient light-dark cycle. It is reasonable to speculate that this is the case with many CFS sufferers given that, even in healthy individuals, natural exposure to light of sufficient intensity and duration to exert an entraining effect is often inadequate (Savides et al., 1986).

Under conditions of inadequate exposure to photic and non-photic agents that facilitate entrainment to the 24-hour day, the rhythm of the SCN will free-run to its intrinsic period that, in humans, tends to be approximately 24.3 to 24.5 hours (Arcndt, 1998a). The result of human free-running is the progressive delaying of the clock relative to the environmental cycle (Wever, 1986). The phase delay in sleep activity rhythms found in the CFS group might, therefore, reflect the occurrence of such a process. The longer
sleep-onset latencies demonstrated in the CFS group are further evidence of a delay in the SCN rhythm, as are later waking times. While increased sleep-latency may be argued to result from increased day-time napping, the opposite result was found in the present CFS group, where napping was associated with shorter nocturnal sleep-onset latencies. Later waking could not be explained by reduced sleep efficiency through the night.

Because no direct measures of the timing of the clock were taken, it is impossible, at this stage, to say whether the 45-minute delay in sleep-activity is indicative of a similar delay in the timing of the SCN rhythm. While it is theoretically possible that reductions in environmental time cues in the CFS group induce a state of complete free-run, this would appear unlikely, as such cues would not be entirely absent. It is more reasonable to suggest that lack of exposure to adequate light-dark and social cues through the day produce a state of partial free-run, or over-running of the SCN rhythm, resulting in it taking longer to get to sleep at night. It may also be that, despite it taking longer to get to sleep, the tendency for CFS patients to maintain similar retiring times to controls assists in preventing continued free-running of the clock and, as such, is an adaptive behaviour.

The significant association found between longer sleep-onset latencies, lower overall activity levels and reduced amplitude of the sleep-activity rhythm is consistent with the idea that chronic over-running of the SCN rhythm may result from a lack of salient non-photic time signals. Sleep-onset latencies in people suffering from sleep-onset insomnia have been found to be related to a phase delay in the core temperature rhythm, which is
commonly used as an indicator of SCN timing (Morris et al., 1989). Although it might be expected that reduced amplitude and mesor of the sleep-activity rhythm would also, therefore, be associated with the overall phase delay in sleep-activity, this need not be so, given that the individual is likely to be striving to maintain behavioural entrainment with their social environment. Normal bed-times, in spite of longer sleep-onset latencies, is again suggestive that this may be the case. As such, longer sleep-onset latencies might be, in some ways, an indicator of magnitude of the over-run of the SCN rhythm relative to the environmental cycle.

In this context, the significant relationship between sleep-onset latency and physical well-being raises the possibility that a delay in the SCN rhythm relative to the sleep-activity cycle contributes to the symptomatology of the disorder. Because sleep-onset latency was also related to reduced activity levels and smaller sleep-activity rhythm amplitude, this relationship could simply reflect the fact that reductions in sleep-activity rhythm amplitude, which have previously been suggested to contribute to sleep-onset latency by causing the SCN rhythm to over-run, are the result of increased levels of disability. However, the significant negative association between sleep-onset latency and physical well-being remained, even when the influence of sleep-activity rhythm amplitude was partialled out.

The overall picture suggested by this line of reasoning is that CFS may be associated with a lack of, or weaker, entrainment of the SCN rhythm to environmental and sleep-wake rhythms. The finding of reduced activity levels and sleep-activity rhythm
amplitudes, and their relationship to sleep-onset latency, supports the view that such weaker entrainment may be brought about by a lack of non-photic time cues. Such a scenario has been suggested by Leese et al. (1996) following their demonstration that the dysregulation of HPA-axis functioning that has been noted in CFS sufferers also occurs in shift-workers following 5 days of night shift. While the sleep-activity rhythm disturbances noted in the CFS group from the current study are by no means as substantial as those associated with working night-shift, they are, however, likely to be chronic, and may interact with individual physiological vulnerabilities. As has been discussed in Chapter 4, it is known that people who remain in shift-work for long periods tend to have more robust systems that allow them to cope better with the abnormal routines (Arcndt, 1998a). Thus, similar levels of internal dysregulation to those described by Leese et al. (1996) in their group of shift workers could, theoretically, result from substantially smaller insults to the circadian systems of more sensitive individuals. Further investigations of circadian functioning are required to more clearly address this proposition. In particular, assessment of the sleep-activity cycle in combination with physiological monitoring is necessary in order to evaluate the relationship between behavioural rhythms and that of the SCN. Those issues are the central subject of the two proceeding studies.

The findings of this study have other important implications for CFS research in general. The 45-minute phase delay in sleep-activity rhythms indicates that CFS patients differ systematically from healthy controls with respect to the phase relationship between the
circadian time to which their internal environment is set and the timing of the environmental light-dark cycle. Given that sleep latencies were longer in the CFS group, this 45-minute delay may understate the actual physiological delay present in CFS patients relative to healthy controls. However, even a 45-minute delay is likely to be enough to alter findings of research in which physiological parameters are compared between people with CFS and healthy controls. At certain times of day, the expression of a number of physiological rhythms can change sharply. One example is cortisol secretion, which rises gradually from the early morning nadir, but very sharply around the time of normal waking, where it peaks and then tends to drop again substantially (Van Cauter et al., 1990). A sharp fall in cortisol levels also commonly occurs in the mid-evening. At both of these times, rises or falls that encompass several standard errors of the mean occur within 15-30 minutes (Van Cauter et al., 1990).

Clearly, the potential exists therefore, for systematic between group differences in phase to substantially confound research findings that do not take them into account. Interestingly, the two sampling times of MacHale et al. (1998) in their study of diurnal variation of cortisol secretion in CFS patients compared to controls were around the times (0:800 and 20:00) when these rapid changes occur. Although MacHale et al. (1998) did not find significant differences between groups, their lower morning and higher evening cortisol levels could be accounted for by a phase delay in the CFS group. Data from another study of cortisol secretion in CFS (Wood et al., 1998), in which hourly samples were collected from 07:00 until 22:00, could also have been confounded
by a systematic phase delay in the CFS group compared to controls. These authors found that, contrary to previous reports of hypocortisolacemia in CFS patients, their group exhibited non-significantly higher levels across the sampling period. If the CFS group were phase delayed by around an hour, and visual inspection of the chart provided by the authors suggests this could have been the case, then sampling would have occurred during a circadian time where cortisol levels were naturally higher.

These examples are provided to illustrate that the kind of systematic phase alterations found in the present study could easily lead to artefactual findings. The example cited here was for cortisol secretion, but many other variables that have been tested in CFS patients would also be subject to confounding by circadian factors. In small samples, the problem would be particularly significant, as even one or two participants who were significantly delayed could have an inordinate influence on findings. The other aspect of this problem involves the higher levels of inter-subject variability in sleep-timing noted in this study. Increased variability is likely to add significant error variance to study protocols and reduce their power to detect real between group differences. It is unlikely that this particular issue is idiosyncratic to CFS research. Potential group differences in circadian phase are rarely taken into account in studies of other states of ill-health. The only foreseeable answer would be to implement even basic monitoring of sleep-wake patterns for, say, five days prior to sampling so that adjustments of procedure could be made to ensure samples were taken at similar circadian times for all participants or, at least, differences could be adjusted for statistically.
CHAPTER 6

STUDY 2: A HOME-BASED STUDY OF THE RELATIONSHIP BETWEEN 24-HOUR SLEEP-ACTIVITY AND CORE TEMPERATURE RHYTHMS IN CFS
Introduction

The major findings of Study 1 were that the CFS group demonstrated abnormalities of their sleep-activity rhythms, in the form of reduced activity levels and amplitude, and an overall phase delay of approximately 45 minutes. The findings that, compared with controls, sleep-onset latencies were longer and waking times later in the CFS group were suggestive that the phase delay in sleep-activity may have been driven by an underlying physiological delay in the timing of the SCN rhythm. Of course, the actual presence, magnitude and consistency of alterations in SCN timing can only be speculated about, given that no direct measure of physiological timing was carried out. However, the relationship detected between increased sleep-onset latencies and decreased physical well-being is suggestive of the possibility that a disturbance in circadian timing might be related in some way to symptomatology.

One hypothesis that could be drawn from the above correlation between increased sleep-onset latencies and poorer physical well-being is that physical symptoms are associated with a phase delay in physiological timing. While a delay (or an advance) in physiological timing is not, in itself, detrimental to the health of an individual, phase alterations relative to environmental time can be problematic due to the person’s internal cycle being at odds with that of the prevailing physical and social environment. Such a
state will almost invariably mean that environmental time cues clash with and confuse circadian regulatory systems, leading to a degree of internal desynchrony. The acute version of this state is exemplified by jet-lag, while shift-work engenders a more chronic state of temporal flux.

Although it can be applied to lack of entrainment between any subset of physiological rhythms, in the circadian literature, the term 'internal desynchrony' has often been used to refer specifically to an abnormal phase-relationship or general dissociation between the rhythm of the hypothalamic clock, and the individual's sleep-activity cycle (Wever, 1986). As discussed in Chapter 4, as well as the clear symptomatic similarities between CFS and known states of internal desynchrony, such as jet lag and shift-work related syndromes, specific physiological and psychological changes that are of direct relevance to CFS have been demonstrated to result from sleep-wake/SCN desynchrony. These include: fragmentation of sleep and wakefulness and altered sleep structure (Dijk & Czeisler, 1994), decreases in cognitive functioning (Dijk, Duffy & Czeisler, 1992) and alertness (Czeisler, Dijk & Duffy, 1994), and depressed mood (Boivan et al., 1997). There is also strong evidence that sleep-wake/SCN synchrony is required for the proper expression of every pituitary and pituitary dependent hormone (Van Cauter, 1990), as well as for normal glucose regulation and insulin secretion (Scheen & Van Cauter, 1998; Simon, 1998). Turek (1994) pointed out that sleep-wake/SCN desynchrony engenders a state of internal temporal dysregulation because rhythms that entrain primarily to the sleep-wake cycle become out of phase with those that entrain primarily to the output
from the SCN. Further, the proper and, presumably, healthy circadian expression of those rhythms that are regulated by the timing of both the sleep-wake and the SCN is particularly undermined.

The results of Study 1, and the fact that the health consequences of states of desynchrony between the sleep-wake cycle and the SCN rhythm have such similarity to the symptomatology of CFS, suggest that an examination of the relationship between these two rhythms is warranted. Clearly, such an examination requires the concurrent monitoring of both rhythms in CFS and comparison groups. Unfortunately, direct measurement of the output of the SCN in vivo is not currently possible and, as such, SCN timing must be inferred from the timing of measurable physiological indicator rhythms such as melatonin secretion or core body temperature (Myers, 1995). The fact that melatonin secretion by the pineal is under the direct neural control of the SCN (Moore, 1996), and its relative stability in the face of various environmental and behavioural challenges (Vaughan, 1986) makes the rhythmic secretion of the hormone one of the most reliable markers of the timing of the endogenous circadian pacemaker (Lewy, 1999). The major drawbacks of the use of melatonin as a marker of circadian timing are practical, in that multiple blood or saliva samples must be collected at half hourly intervals over an extended period (at least several hours during the early to mid evening), and these then require analysis by professional laboratory staff with specialised equipment.
Another marker rhythm that is used commonly is that of core temperature (CT). The human core temperature rhythm is inversely related to that of melatonin secretion (Myers, 1995). In a typical, healthy individual, with regular sleep-wake habits, the core temperature rhythm generally commences rising from its low-point of around 36.5°C about 3 hours before waking, continuing until it peaks at around 37.4°C approximately 3 hours before retiring (Refinetti & Menaker, 1992). While there is strong evidence to indicate that the core temperature rhythm is regulated at least to some extent by melatonin, inconsistencies and gaps in the literature remain which prevent the conclusion that the core temperature rhythm is fully dependent on the rhythm of melatonin secretion (Cagnacci, Krauchi, Wirz-Justice & Volpe, 1997). Regardless of whether the rhythms of melatonin secretion and core temperature are different ‘hands’ of the endogenous pacemaker (Myers, 1995), or different sides of the same hand, the core temperature rhythm has been widely used as a marker of the endogenous timing (Refinetti & Menaker, 1992).

As an alternative indicator of circadian timing to melatonin secretion, core body temperature has several advantages. Although monitoring is moderately invasive (eg. through rectal, tympanic or ingestible thermistors), it can be carried out continuously, while participants are sleeping or active, and the data are almost instantly downloadable and available. The major drawback of using core temperature rather than melatonin secretion as an indicator of circadian timing, is the fact that a greater range of factors obscure the endogenously driven component of the core temperature rhythm. While
factors that directly affect the functioning of the clock, such as lighting intensity, timing and duration, still require attention, other factors such as food intake, sleep and physical activity produce changes in core temperature and, therefore, 'mask' core temperature variation that is driven purely by the clock (Minors & Waterhouse, 1989). Factors that impede heat loss, such as ambient temperature and amount and type of clothing can also mask the endogenous component of the core temperature rhythm (Refinetti & Menaker, 1992).

Constant routine protocols, in which subjects are monitored for at least 24 hours, and during which they must remain awake and sedentary in constant environmental conditions (Minors & Waterhouse, 1984) have been used to remove the effect of masking factors upon the core temperature rhythm. However, while constant routines are regarded as the 'gold standard' in circadian research, they are arduous for even the healthiest of individuals, and their use with patient groups is problematic for both practical and ethical reasons. In cases such as CFS, where people suffer pernicious fatigue as a result of physical and/or mental stress, there is also potential for problems arising with respect to the validity of data obtained under such a regimen.

In recent times, a number of groups have developed alternatives to constant routines, some in which subjects are at least permitted to sleep (Carrier & Monk, 1997), and others in which the sleep-activity behaviour of subjects is not restricted at all (Minors & Waterhouse, 1992). These methods rely on the monitoring of sleep or sleep and activity
levels during the temperature data collection period, and then applying various formulae to correct the raw data, so that the temperature component that is due to exogenous factors is removed. The process has been referred to as ‘purification’ (Minors & Waterhouse, 1992, p.68). It is beyond the scope of this chapter to provide a detailed discussion of the relative merits of the numerous purification techniques that have been published, or their efficacy compared to constant routines (for reviews, see Klerman, Lee, Czeisler & Kronauer, 1999; Minors & Waterhouse, 1992; Waterhouse et al., 1999). However, given that there is no question that the use of raw temperature data collected in uncontrolled conditions to estimate the phase of the endogenous circadian oscillator is invalid, and that the use of a constant routine protocol is impractical for many CFS sufferers, purification techniques are an attractive alternative.

Two techniques that attempt to purify the core temperature data of fully ambulatory subjects have been published and validated by the same group in Britain (Waterhouse et al., 1999). The first technique, is called ‘purification by categories’ while the second, more recent technique is called ‘purification by intercepts’. Purification by categories is carried out by first dividing temperature and activity data into 30-minute bins. Activity data, which may have been collected via log-book or actimetry (in the current study, body activity counts collected by actimetry were used), is divided into 16 equal categories between the minimum and maximum half-hourly counts. The first category is treated as sleep, and a positive correction is applied to the data to account for the cooling effect of sleep. The second is treated as lying down but awake, and no correction is
applied as it is assumed that there is no masking effect. The remaining 14 categories are for the graduated levels of waking activity, and the negative correction applied increases with the associated increases in activity. Correction coefficients are calculated for each category and applied iteratively to the raw data so that the temperature profile approximates gradually more closely to a cosine curve, which is assumed to better represent the endogenous component. Finally, cosinor analysis is applied to the purified data in order to obtain the parameters of mesor, phase, amplitude and goodness of fit. This method has been published and demonstrated several times over the past decade (Minors & Waterhouse, 1989, Minors & Waterhouse, 1992, Waterhouse et al., 1999).

Purification by intercepts differs from the process of purification by categories, primarily in that the amount of the correction applied to half-hourly raw temperature means is determined by linear regression, rather than by iterative approximation to a cosine curve. The 240 6-minute temperature data points are divided into 48 overlapping 3-hour sections. Each section is then matched with the summed activity over the previous 30-minutes and the correlation between the two is calculated. If the correlation coefficient is not significantly different from zero, then the mean of the temperatures is used, as it is assumed that activity had no impact upon core temperature at that point. If the correlation coefficient is significantly different from zero, then linear regression of activity upon temperature is carried out. The $\beta$-coefficient and intercept, and an extrapolated temperature associated with no activity, is calculated. Because sleep is associated with a drop in temperature that is greater than simple inactivity, all core
temperature values collected from 30 minutes after retiring until 30 minutes before rising are increased by 0.23°C. Finally, cosinor analysis is applied as in the purification by categories method, to obtain rhythm parameters.

A recent assessment of the validity of purification techniques compared to constant routines for the measurement of the endogenous core temperature rhythm has argued that linear demasking techniques are unreliable (Klerman et al., 1999). However, the techniques tested were considerably more blunt than those described above. Further, the assessment involved comparing the results of constant routine and purified temperature data, even though the data that were purified were obtained from participants who were ambulatory while awake. This is somewhat problematic, as three of the four demasking techniques tested were designed only to account for masking factors associated with sleep, and all were applied only during scheduled or actual sleep-times. Thus, the impact of physical activity and food intake, both of which are tightly controlled during a constant routine, were not addressed by the demasking techniques applied. There can be little doubt that this had a significant impact on the comparative validity of the results and, subsequently, the authors’ conclusions. Their central point, however, that linear demasking techniques erroneously assume that the masking effects of sleep on the core temperature rhythm are the same regardless of the circadian time at which sleep occurs is important, and further research and development is required.
In contrast to the conclusions of Klerman et al. (1999), a recent validation and comparison of the two purification methods described in detail above found that both methods appeared to remove the exogenously produced component of the core temperature rhythm almost completely, and that the newer purification by intercepts method was at least as effective as purification by 16 categories (Waterhouse et al., 1999). As with Klerman et al. (1999), this study used a forced desynchrony protocol, which tested the effects of purification of sleep and ambulatory data, collected at continuously changing phase positions relative to the rhythm of the endogenous pacemaker. As such, it is difficult to argue that the concerns expressed by Klerman et al. (1999) regarding the linear demasking techniques tested in their protocol would also apply to these newer, more comprehensive techniques.

The following study was undertaken in order to investigate several aspects of physiological timing in CFS, and its relationship to the rhythm of sleep-wake. The endogenous (purified) core temperature rhythm was monitored over several days, in order to provide an indication of the timing of the SCN rhythm, in a group of CFS patients and a group of healthy controls matched for age and sex. Three main questions were to be addressed by the protocol:

1. Are there any systematic differences between CFS and healthy individuals in the expression of the endogenous core temperature rhythm? The specific parameters
that were assessed over three-days and compared between groups were phase, mesor, amplitude and goodness of fit to a cosine function with a 24-hour period.

2. Is the timing of the endogenous core temperature rhythm less stable from day to day in CFS patients? This question was addressed by comparing the variability of the timing of the core temperature rhythm over the three days.

3. Is the relationship between the endogenously driven core temperature rhythm and sleep-wake weaker in CFS patients? This question was examined by comparing the correlations between the phase positions of sleep-wake and core temperature in the two groups.

Method

Participants

CFS sufferers were recruited in the same manner as in Study 1. Twelve CFS sufferers were admitted to the study (4 male and 8 female), with a mean age of 33.5 years \( (SD=11.4) \). Twelve control participants were recruited by word of mouth to match the CFS group for age \( (M=32.5 \text{ years, } SD=9.6) \), sex and work status. Healthy controls were paid for their participation.
Materials and Procedure

In order to measure their sleep-activity patterns, all participants were required to fill out the same sleep-activity log-book as in Study 1 for two weeks. Core temperature monitoring was carried out in the second week, when participants wore activity and temperature loggers (Mini-logger 2000, Minimitter, Sun River, OR) that recorded body movement frequency and rectal temperature (Rectal Probes: Cincinnati Sub-Zero, OH, USA) every minute for 72 hours. This monitoring was done while participants carried on with their usual daily routines in their own environments. CFS and control participants were tested at the same time, in order to match for seasonal and weather patterns.

At the end of the two weeks, participants completed the Beck Depression Inventory-II (BDI) (Beck, & Steer, 1996) in order to provide an indication of depressive symptoms over the monitoring period. The BDI is a 21-item instrument that is designed to assess for the presence of clinically significant depression. The BDI was used primarily as a way of assessing for the presence of depressive symptomatology so that the effects of depression could be controlled for where necessary in statistical analyses. The BDI is particularly suitable for this purpose because its item content directly reflects much of
the symptom criteria for major depressive illness outlined in the DSM-IV (American Psychiatric Association, 1994; Beck & Stecr, 1996).

Temperature data from one female control participant was lost due to equipment failure, and from one female CFS participant because of frequent probe slippage or removal that led to the loss of too many data points to make a reliable estimation of temperature rhythm parameters. Probe slippage or removal also meant that, for two participants from each group, only two full days of data were useable. Thus, raw temperature data from 22 participants were cleaned to remove intermittent invalid temperature values associated with probe removal or slippage. These values were recoded as missing. The electronically monitored core temperature and body movement frequency, which were recorded at 1-minute intervals, were recoded into 6-minute bins in preparation for the purification process.

Purification by 16 Categories and by Intercepts methods (Waterhouse et al., 1999) was carried out using dedicated software written in GWBASIC (provided by Waterhouse). Each participant’s 72 hours of temperature and activity data were divided into three 24-hour sections (2 sections for those with only two days of data), which were then purified separately. Sleep and wake times for each of the three days, taken from log-books, were also entered as required for Purification by Intercepts. The program then calculated the masking effect of sleep-activity patterns by regressing activity data (collected via the
activity monitors) against temperature in the manner of each method, as described in the
troduction. Corrected, or ‘unmasked’ temperature values were then submitted to
cosinor analysis in order to provide summary measures of mesor, amplitude, phase and
goodness of fit.

Data from the 14 days of self monitoring of sleep-activity were analyzed via non-linear
least squares regression using a software package (Cosifit, Circesoft, Waltham, MA,
USA) developed specifically for the analysis of circadian rhythm data (Teicher &
Barber, 1990). This procedure provided the rhythm parameters of amplitude, phase,
mesor and goodness of fit to a 24-hour period ($r^2$) for the sleep-activity rhythms of each
participant. In order to look specifically at the relationship between core temperature
and the sleep rhythm timing, the cosine fit was also carried out on the data when it was
coded only to indicate when the individual was asleep or awake, i.e., regardless of their
activity level (referred to as ‘sleep-wake’ henceforth). This was done because it is the
timing of sleep relative to SCN phase that is primarily indicated in the literature as being
of central importance to rhythm expression (Turek, 1994; Van Cauter, 1990), and
because estimates of sleep-phase based on sleep-activity rhythms are likely to be
systematically affected by reduced daytime activity levels in CFS patients compared to
controls. Thus, sleep-acrophase was calculated for each participant in order to
determine the relationship between sleep and temperature rhythms. Sleep mesor was
also calculated as it indicated the amount of time spent in sleep.
Results

The parameters of mesor, phase, amplitude and the $r^2$ for the cosine fits for sleep-activity and sleep-wake data were treated as dependent measures in two separate MANOVAs, with group (Control vs CFS) as the independent variable (IV). A similar procedure was followed for the temperature rhythm parameters, and MANOVAs were conducted upon the raw data, and the data obtained via each of the two purification methods. Means and standard deviations are summarized in Table 6.1. As in Study 1, data from the two-week sleep-activity logs were coded on a 7-point ordinal scale, with -3 representing sleep, -1 for rest, 1 for sedentary activity and 3 for significant physical movement. Sleep-wake is a significantly altered coding of the data from logs, with rest, sedentary and physical activity all coded as 0 for awake, and sleep coded as 3. Thus, the sleep-wake acrophase represents the sleep mid-point, and a mesor of 1 would indicate that a person slept, on average, for 8 hours per day.

It has been demonstrated that the luteal phase of the menstrual cycle is associated with changes in the core temperature profile in the form of a higher mesor, flatter amplitude and phase delay (Leibenluft, Fiero & Rubinow, 1994). As there is a high degree of inter-individual variability in the length of the various phases within the menstrual cycle (Leibenluft, Fiero & Rubinow, 1994), and it was not possible to test whether ovulation had occurred, statistical means to control for these potentially confounding effects were employed. Those participants with a regular menstrual cycle and who were 14 days or
Less from their next estimated first day of menstruation were classified as being in the luteal phase.

All other participants were classified as not being in the luteal phase. By this method, there were three women classified as being in the luteal phase in the control group compared to two in the CFS group, and so menstrual phase was tested for its significance as a covariate in the analysis of the temperature data. It was found to have a significant effect (p<.05), and was, therefore included as a covariate. Although depression (BDI) scores were significantly higher (t=7.01, p<.001) in the CFS group (M=12.81, SD=3.84) than for controls (M=3.36, SD=2.29), they did not function as a significant covariate in any of the following analyses and were, therefore, not included.

**Comparison of Sleep-Activity Rhythms**

MANOVA found that sleep-activity patterns obtained from the two-week sleep-activity logs differed significantly between the two groups F(3,17)=10.82, p<.001 (see Table 6.1). Univariate ANOVAs found that the CFS group had a significantly lower sleep-activity mesor F(1,20)=38.97, p<.001, and flatter amplitude F(1,20)=4.22, p<.05. This indicates that the CFS group was less active overall and that the difference between day and night was less pronounced. No significant overall difference between groups were found for sleep-wake F(2,19)=3.16, p>.05. The non-significant trend was, however, for the CFS group to spend about an hour longer in sleep (490 mins per day) compared to controls (432 mins per day: see Table 6.1).
Table 6.1.
Means and standard deviations for sleep-activity, sleep-wake and core temperature (raw, purified by categories, and purified by intercepts methods) parameters for CFS and Healthy control groups.

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th></th>
<th>CFS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td><strong>Sleep-Activity Parameters</strong>*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesor</td>
<td>.30</td>
<td>.20</td>
<td>.35</td>
<td>.27</td>
</tr>
<tr>
<td>Phase</td>
<td>15:19</td>
<td>0:52</td>
<td>15:37</td>
<td>1:23</td>
</tr>
<tr>
<td>Amplitude</td>
<td>2.58</td>
<td>.27</td>
<td>2.21</td>
<td>.52</td>
</tr>
<tr>
<td>r-squared</td>
<td>.74</td>
<td>.05</td>
<td>.75</td>
<td>.04</td>
</tr>
<tr>
<td><strong>Sleep-Wake Parameters</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesor</td>
<td>.90</td>
<td>.09</td>
<td>1.02</td>
<td>.15</td>
</tr>
<tr>
<td>Phase</td>
<td>4:01</td>
<td>0:40</td>
<td>4:01</td>
<td>1:05</td>
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<tr>
<td><strong>Temperature Rhythm Parameters:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Raw Data</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesor</td>
<td>37.05</td>
<td>.17</td>
<td>36.91</td>
<td>.17</td>
</tr>
<tr>
<td>Phase</td>
<td>15:48</td>
<td>1:26</td>
<td>15:18</td>
<td>1:48</td>
</tr>
<tr>
<td>Amplitude</td>
<td>.46</td>
<td>.11</td>
<td>.42</td>
<td>.13</td>
</tr>
<tr>
<td>r-squared</td>
<td>.72</td>
<td>.09</td>
<td>.64</td>
<td>.21</td>
</tr>
<tr>
<td><strong>Data purified by Categories</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesor</td>
<td>36.98</td>
<td>.17</td>
<td>36.85</td>
<td>.17</td>
</tr>
<tr>
<td>Phase</td>
<td>16:01</td>
<td>1:30</td>
<td>14:58</td>
<td>1:54</td>
</tr>
<tr>
<td>Amplitude</td>
<td>.35</td>
<td>.10</td>
<td>.35</td>
<td>.14</td>
</tr>
<tr>
<td>r-squared</td>
<td>.73</td>
<td>.10</td>
<td>.64</td>
<td>.23</td>
</tr>
<tr>
<td><strong>Data purified by Intercepts</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesor</td>
<td>37.01</td>
<td>.18</td>
<td>36.86</td>
<td>.20</td>
</tr>
<tr>
<td>Phase</td>
<td>16:25</td>
<td>2:37</td>
<td>14:08</td>
<td>4:11</td>
</tr>
<tr>
<td>Amplitude</td>
<td>.36</td>
<td>.12</td>
<td>.31</td>
<td>.14</td>
</tr>
<tr>
<td>r-squared</td>
<td>.61</td>
<td>.18</td>
<td>.55</td>
<td>.24</td>
</tr>
</tbody>
</table>

* p < .05; ** p < .01; *** p < .001

*Comparison of Core Temperature Rhythms*

When analysed via MANCOVA, with menstrual phase as the covariate, rhythm parameters for core temperature did not differ between the groups: these results were the same whether the data used were raw F(4,16)=1.28, p>.05, purified by category
$F(4,16)=1.32, p>.05$ or purified by intercepts $F(4,16)=1.24, p>.05$ (see Table 6.1). This indicates that the core temperature rhythms of CFS and control groups did not differ with respect to their mesor, phase, amplitude nor the goodness of fit to a 24-hour cycle. Although not significant, purified temperatures were lower in CFS participants, and the acrophase of the temperature rhythm was earlier. CFS acrophases were earlier by around an hour when purified by categories, and over two hours when purified by intercepts. Even with a relatively influential (outlying) point removed from the CFS group, the trend remained for the mean CFS temperature rhythm to be advanced by around an hour using either purification method.

**Stability of the Core Temperature Rhythm**

Inter-day stability of the core temperature rhythm was assessed by calculating the variability (variance) of the timing of the temperature acrophase for each participant over the three-day monitoring period. This procedure was carried out for raw and purified data, and variances averaged across the groups. Results are presented in Table 6.2, and it can be seen that, compared with controls, variances (expressed in hours) appeared to be lower for the CFS group for raw data and that purified by categories. These inter-day stability measures for raw and purified data were then analysed as dependent variables in MANOVA, with the result indicating that no significant overall differences existed between groups $F(3,18)=0.28, p>.05$. Thus, the timing of the core temperature rhythm was no more stable in CFS compared to control participants over the three days of monitoring.
Table 6.2.
Group means and standard deviations for inter-day variability (variance, expressed in hours) of the timing of the acrophase of the raw and purified core temperature data over the three days.

<table>
<thead>
<tr>
<th></th>
<th>Raw Data</th>
<th>Purified by categories</th>
<th>Purified by intercepts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M</td>
<td>SD</td>
<td>M</td>
</tr>
<tr>
<td>Control</td>
<td>.61</td>
<td>.43</td>
<td>1.19</td>
</tr>
<tr>
<td>CFS</td>
<td>.59</td>
<td>.63</td>
<td>1.10</td>
</tr>
</tbody>
</table>

*p ≤ .05, **p ≤ .01, ***p ≤ .001.

Consistency of the Relationship Between Sleep-Wake and Core Temperature Rhythms

Consistency of the relationship between the internal pacemaker and sleep-wake cycle was assessed by correlating sleep and temperature acrophase for each group. Analyses were conducted using sleep-wake acrophase calculated from log-book data, and core temperature acrophases calculated from raw data, as well as that purified by categories and intercepts. Scatterplots are presented in Figure 6.1. Correlations were calculated with the effects of menstrual phase partialled out, and results are presented in Table 6.3. The difference between CFS and control correlation coefficients was tested using Fisher’s Z (Howell, 1982). This procedure found that the correlation between sleep and core temperature acrophase was significantly better for controls than for the CFS group.
Figure 6.1 Scatterplots of the relationships between the acrophases of core temperature and sleep-activity rhythms for each individual for raw core temperature data (A), core temperature purified using the 16-category method (B) and core temperature purified using purification by intercepts.
Table 6.3.
Correlations between sleep-wake and core temperature acrophases for CFS and healthy control groups. Partial correlations, controlling for menstrual phase, are presented when temperature data are raw, purified by the 16-category method, and purified by the intercept method.

<table>
<thead>
<tr>
<th></th>
<th>Unpurified temperature data</th>
<th>Temperature data purified by categories</th>
<th>Temperature data purified by intercepts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>.91 ***</td>
<td>.90 ***</td>
<td>.85 ***</td>
</tr>
<tr>
<td>CFS</td>
<td>.79 ***</td>
<td>.54</td>
<td>.17</td>
</tr>
</tbody>
</table>

* p<.05; ** p<.01; *** p<.001

(Z=2.17, p<.05), when data were purified by intercepts. This became non-significant when the CFS correlation coefficient used was calculated without the extremely phase-advanced participant (Z=1.58, p>.05). When data were purified by categories, the differences between coefficients did not attain significance (Z=1.74, p>.05).

**Discussion**

As was the case in Study 1, the sleep-activity rhythms of CFS sufferers had a lower mesor, and lower amplitude. In contrast with the results of the earlier study, however, no evidence of an overall phase delay in sleep-activity was found. The timing of sleep was similar between groups, and there was a non-significant trend for CFS participants to sleep about an hour longer, on average. Circadian rhythms of core temperature did not
differ overall between the CFS and Control groups on any of the parameters measured, that is, phase, amplitude, mesor and goodness of fit to a 24-hour period. Although it did not attain significance, there was a trend for CFS participants' temperature rhythms to be phase advanced by around an hour, on average. There was no evidence that the timing of the core temperature rhythm was any less stable between days in the CFS group. A significant positive relationship was found between the timing of core temperature and sleep-wake rhythms in control participants whether core temperature data was raw, or when it was purified to remove the exogenous influences of the sleep-activity cycle. For the CFS group, correlation coefficients were lower regardless of how the temperature data were treated and, when purified, coefficients became non-significant.

Given the nature of the illness, reduced sleep-activity mesor and amplitude in the CFS group were expected, and support the conclusion from Study 1; that the difference between day and night in terms of sleep-activity patterns is less pronounced in CFS sufferers and that this might indicate that fewer non-photic cues were available to the SCN. The lack of phase delay in sleep-activity rhythms of the CFS participants is inconsistent with the findings of the earlier study. While this may be due in some part to the substantially lower number of participants compared to the first study, it reaffirms the apparently intrinsic heterogeneity of the patient group being investigated.

Low numbers of participants also resulted in reduced power to detect differences in the core temperature rhythm. Core temperature mesor was consistently lower in the CFS
group, and the rhythm tended towards a phase advance. It is clear that, in any comparison between active and inactive individuals, raw temperature data will be higher due to the direct effects of activity. The production of body heat is directly related to metabolic rate (Bowman & Rand, 1982) and it is also possible that, in CFS, reduced metabolic activity and muscle mass, resulting from a less active life-style may cause reduced heat production, even at rest. The trend towards a phase advance is directly counter to the suggestion from Study 1, that lack of non-photic cues due to a less salient sleep-activity rhythm would cause the rhythm of the SCN to over-run and, therefore, be somewhat phase delayed. Clearly, the answer is unlikely to be so straight-forward. Low participant numbers again limit the emphasis that can be put on any findings, especially non-significant ones. However, the trend to early temperature acrophases in the CFS group is quite apparent (see Figure 6.1) and, in this case, it may be that increased numbers of participants may have brought it to significance, rather than have obscured it.

The possibility of a consistent phase advance rather than delay in the temperature rhythm relative to sleep-wake is, in some ways, more interesting in that it could explain some of the phenomenology of CFS, such as disturbed sleep and depressed mood. When a group of investigators artificially produced such a state of sleep-SCN desynchrony in healthy participants by delaying their sleep phase, they found evidence of shorter REM latencies, early waking, and depressive mood changes (Surridge, MacLean, Coulter & Knowles, 1987). It is well-known that sleep occurring on the rising limb of the core temperature
rhythm is more disturbed than sleep occurring on the descending limb (Dijk & Czeisler, 1995). Nevertheless, the evaluation of the relevance of these findings to CFS awaits larger, more controlled studies.

The purification technique that was used made little difference to the temperature rhythm parameters obtained for control participants, or their relationship to sleep-wake. However, for the CFS group data, purification by intercepts resulted in greater variability with respect to acrophase, and a markedly lower correlation between core temperature and sleep-wake acrophases, than that calculated via the purification by categories method. This is likely to be due to the fact that the purification by categories method assumes that the most inactive category is sleep and, although this may be a reasonably safe assumption for healthy, normally active people, it may not be as reliable when people are often inactive while awake, as is the case with many CFS patients. In such circumstances, the ‘sleep’ category may be assigned not only to periods of actual sleep, but also to times when the individual is awake but inactive. The negative mask that is intended to control for sleep would thus be calculated on the basis of sleeping and waking times, which would, most probably, lead to a decrease in the size of the correction factor and its application to both sleep and inactive waking periods. Perusal of the data and the masks calculated via the categories method suggested that this did occur frequently with CFS patients, and only rarely with controls. The problem was likely to have been compounded by the fact that, while Minors and Waterhouse (1989; 1992) have typically used wrist actimetry to monitor activity, actimeters in this study
were placed around participants’ waists. This is less likely to successfully distinguish between periods of sleep and periods of waking inactivity. As such, the purification by categories method may have less effectively removed the exogenous component of the core temperature rhythm for the CFS group, and the purification by intercepts, in which actual sleep-times are entered, may, therefore, be a more valid indicator.

Even so, both purification methods led to a substantially lower correlation between the sleep-wake and core temperature rhythms. While the difference between the two groups’ coefficients did not attain significance when the method of purification by categories was used, the actual difference between the coefficients is quite stark. The partial correlation between the sleep-wake and core temperature rhythms was 0.90 for the control group, indicating that 81% of the variability in the timing of one rhythm is accounted for by the timing of the other. In the CFS group, the coefficient of 0.54 indicates that only 29% of the variance is accounted for. Using the coefficients calculated from data purified by intercepts makes for even more substantial differences.

These findings offer some support for the hypothesis that sleep-wake/SCN desynchrony is present in at least some cases of CFS. This, in turn, supports the suggestions by Moldofsky (1995) and Leese et al. (1996) that circadian abnormalities associated with sleep-wake and physiological timing are associated with CFS. It is beyond the scope of the present study to establish any link between circadian abnormalities and the symptoms of the illness. In theory, however, desynchrony between the sleep-activity cycle and the rhythm of the SCN may explain why the CFS group examined by Williams
et al. (1996) showed dissociation between the rhythms of core temperature and plasma melatonin, which are both driven by SCN. Core temperature is determined by the balance of heat production and heat loss. The daily rhythms of heat production and heat loss are, generally, in consistent phase relationship with each other, with the heat loss rhythm lagging just behind that of heat production (Cagnacci et al., 1997). However, it has been reported that the heat loss from extremities is directly associated with sleep onset, and can become dissociated from the core temperature rhythm when the SCN and sleep-activity rhythms desynchronize under free-running conditions. This finding has been used to argue that the SCN drives the core temperature rhythm mainly through its influence on heat production (Cagnacci et al., 1997).

If the sleep-activity cycle is out of phase with the SCN rhythm, a state may arise where the rhythms of heat production and heat loss are not in proper phase relationship, which would then alter the expression of the core temperature rhythm. Clearly, this presents a conundrum for the current investigation, in which the core temperature rhythm was used as an indicator of SCN function. However, even if the lack of correlation between core temperature and sleep-activity rhythms in CFS sufferers was due to the circadian component of the temperature rhythm being obscured by heat production/loss desynchrony, this still suggests, albeit indirectly, the presence of underlying SCN/sleep-activity desynchrony.

Regardless of the underlying cause(s) of circadian abnormalities in people who suffer from CFS, many of the implications, for both patients and researchers, are similar.
Firstly, the health consequences may be significant, since such desynchrony is likely to undermine the proper circadian expression of a number of physiological and behavioral parameters (Turek, 1994). This, in turn, could chronically undermine the health of the individual and contribute to the maintenance of the disorder. Second, CFS research that focuses on parameters subject to circadian variation has the difficult task of taking circadian dysregulation into consideration. If the lack of relationship between sleep-activity and SCN rhythms found here is generalisable, this could mean that even assessment of participants' sleep-wake schedules may not lead to the removal of circadian factors as a nuisance variable. Increased amounts of error variance associated with these problems may mean that larger than usual sample sizes are required in order to obtain reliable results.

Low participant numbers and the lack of environmental controls means that the results of this study can only offer an indication of the kinds of abnormalities that require further study. A study along similar lines but with larger participant numbers and conducted under more controlled conditions would offer increased sensitivity, and may allow aspects of circadian dysfunction to be investigated in relation to symptomatology. Studying circadian functioning under constant conditions for all participants with respect to activity, food intake, light exposure and ambient temperature may also provide some indication as to whether abnormalities are environment/lifestyle driven or pathological in nature. Such a study will be described in the next chapter.
CHAPTER 7

STUDY 3: A LABORATORY-BASED ASSESSMENT OF THE RELATIONSHIP BETWEEN SLEEP-ACTIVITY CORE TEMPERATURE RHYTHMS IN CFS
Introduction

The findings of the two preceding studies have offered some support for the hypothesis that CFS is associated with altered circadian functioning. In behavioural terms, CFS patients, in comparison with healthy controls, demonstrated significantly lower activity levels and reduced amplitude of the sleep-activity rhythm. A phase delay in the sleep-activity patterns of the CFS group in Study 1 was not replicated in Study 2. In physiological terms, the CFS group tested in Study 2 actually tended more towards a phase advance of their core temperature cycle relative to controls. Study 2 did, however, offer some evidence to support the hypothesis that CFS is associated with a state of internal desynchrony, in that sleep-wake and core temperature rhythms appeared to be more loosely associated in the CFS group.

However, the findings of Study 2, in particular, need to be interpreted in the context of relatively small sample size and a lack of environmental controls. Variations in light exposure, ambient temperature, and meal timing are all factors that are likely to have obscured the endogenously (SCN) driven component of the core temperature rhythm to
some extent and, therefore, limit any conclusions that can be drawn regarding the possible presence of either external or internal desynchrony.

There was, therefore, a need to design a study in which the relationship between the core temperature rhythm and sleep-wake could be examined in a larger group of CFS patients under tightly controlled conditions; where physical activity, meal times, lighting and ambient temperature were held constant. While it was argued, in Study 2, that the use of a constant routine protocol is too arduous for many CFS patients, a compromise method is available, in which participants are monitored in the laboratory but allowed to sleep. Carrier and Monk (1997) tested such a protocol, in which core temperature data collected under such conditions were purified to remove the effects of sleep only. The authors reported that the results of collecting and treating temperature data in this fashion did not differ significantly from results based on data collected from the same participants during a constant routine. More recently, Waterhouse et al. (1999) reported results no different to those collected using a constant routine, using their purification techniques (Purification by 16 Categories and Purification by Intercepts) applied to data collected under conditions similar to those described by Carrier and Monk (1997). These findings indicated that controlling environmental factors that have the capability of masking the endogenous component of the core temperature rhythm, while purifying for the masking effects associated with sleep, is likely to produce an accurate estimation of the timing of the SCN rhythm without having to put participants through the mental and physical stress associated with a constant routine.
Thus, the following study employed such a protocol in order to achieve three aims, which were:

1. To examine whether the Study 2 findings of a looser association between sleep-wake and core temperature rhythms in CFS patients compared to controls could be replicated, and perhaps even extended with a larger sample of participants tested in under controlled conditions.

2. To assess whether the phase relationships between sleep-wake and physiological rhythms in CFS participants were systematically altered, either by a phase delay in physiological timing, as suggested by Study 1, or the possible phase advance suggested by the trends noted in Study 2.

3. To explore whether alterations in circadian functioning were related to CFS symptomatology, namely: number of reported somatic complaints, levels of fatigue and subjectively assessed cognitive functioning.
Method

Participants

The CFS group for this study was comprised of 19 patients who were recruited using the same procedures and criteria as for the previous two investigations. The sample was made up of 4 male and 15 female participants, with a mean age of 40.63 years (SD=13.66). On average, participants in this group completed 11.26 hours (SD=13.68) of paid work per week. Nineteen healthy control participants were recruited by advertisement and word of mouth to match the CFS group for age (M=37.89 years, SD=13.78), sex (4 male and 15 female), and hours of paid work per week (M=12.00, SD=13.34).

Materials and Procedure

As is the two previous studies, all participants completed the sleep-activity log-book for two weeks. Core temperature monitoring was carried out at the end of the second week, while participants spent 26 hours in the Chronic Fatigue Syndrome Laboratory. Participants arrived at approximately 11:30am. After being familiarised with the laboratory surroundings and procedure, participants were provided with rectal thermistors (Cincinnati Sub-Zero, OH, USA), and instructed on how to insert and secure them. Participants inserted their probes and monitors were fitted and started by 12pm.
Data loggers (Minilogger 2000, Minimitter, Sun River, OR, USA) recorded leg and body movement frequency and rectal temperature at one-minute intervals for the next 25 hours. During this time, participants remained sedentary in reclining chairs (until retiring time), or in bed (between retiring and rising time). They were free to watch videos, read or talk during waking hours. The only times participants were not completely sedentary were for toilet breaks and at retiring and rising. Food was offered at specific times (14:00, 17:00, 20:00, 23:00, 02:00, 05:00, 08:00, 11:00 and 14:00) until retiring and then again after rising. A record of food intake was kept for each participant and between-group comparisons indicated no significant between group differences in food intake with respect to the overall amount eaten, and in the distribution of eating across the 24-hour period.

Retiring and rising time was calculated, for each participant respectively, as the median of sleep and wake times recorded in their sleep-activity log-book data for the previous 2 weeks. Participants retired 30 minutes prior to their median sleep time, and were woken at their median wake time. Rising time was a half-hour after waking, with participants being spoken to briefly by the researcher at 15 minutes after waking and then at rising time to facilitate this. During the entire procedure, ambient lighting was maintained at below 15 lux and ambient temperature at 21°C (±1.5°C). Testing was started in the southern hemispheric winter in 1998 and continued until the winter of 1999. A maximum of 4 participants were tested at any one time, and, where possible, an equal number of controls and CFS participants were tested simultaneously. Testing of groups
was distributed evenly over the year so that seasonal factors could be eliminated as a
nuisance variable. While it was originally intended to recruit 20 participants per group
for the study, several factors intervened to prevent this. Probe slippage led to the loss of
too many data points to make reliable assessments of the core temperature rhythms of
two controls and one CFS participant. Non-compliance with various aspects of the
protocol, including the prescribed sleep-activity monitoring procedure, led to the
exclusion of another control participant. Due to difficulties in recruiting replacement
participants who met the CDC criteria (Fukuda et al., 1994) and who were willing to
undertake the procedure, the time available for completion of the study expired before
the final pair could be tested.

Upon arrival, participants were asked to fill out the Beck Depression Inventory (BDI:
Beck & Steer, 1996) and the Profile of Mood States (POMS: McNair, Lorr &
Droppelman, 1981). As was the case in Study 2, the BDI was used as an objective
measure of level of depression so that this could be controlled for when analysing
between and within group data. The POMS consists of 65 adjectives describing feeling
and mood, which are responded to on a five-point scale. The variables measured are
tension–anxiety, depression–dejection, anger–hostility, vigour–activity, fatigue–inertia,
and confusion–bewilderment. For the purposes of the current study, the three subscales
that are most relevant to the symptomatology of CFS were used. These were vigour–
activity (Vigour), fatigue–inertia (Fatigue) and confusion–bewilderment (Confusion).
Participants were asked to respond to items on the BDI and POMS on the basis of how they had generally felt over the previous two weeks; i.e., the period of sleep-activity monitoring. The number somatic symptoms, the number of symptoms endorsed out of 23 critical items identified by Lachar and Wrobel (1979) as representing the Somatic Symptom content area on the MMPI-2 was also used as an indicator of the number of somatic symptoms experienced by participants. CFS participants had already filled out the MMPI-2 as part of the assessment process for entry into the study, while controls were asked to complete the instrument at the time of recruitment. The rationale for the use of the POMS and MMPI-2 scales, rather than instruments that were specific to CFS, was that they could be reasonably answered by both health controls and CFS participants.

As in the previous studies, the 14-day sleep-activity profile from the logbooks was analysed using a software package (Cosifit, Circesoft, Waltham, MA, USA) developed specifically for the analysis of biological rhythm data (Ticcher & Barber, 1990). This procedure provided the rhythm parameters of amplitude, phase, mesor and goodness of fit to a 24-hour period ($r^2$) for the sleep-activity rhythms of each participant. As was the case in Study 2, the cosine fitting procedure was also carried out on data coded only to indicate when the individual was asleep or awake, i.e., regardless of their activity level (referred to as ‘sleep-wake’ henceforth). As discussed in Study 2, this was done because it is the timing of sleep relative to SCN phase that is primarily indicated in the literature as being of central importance to rhythm expression (Turek, 1994; Van Cauter, 1990),
and because estimates of sleep-phase based on sleep-activity rhythms are likely to be systematically affected by reduced daytime activity levels in CFS patients compared to controls.

Due to the fact that that activity associated with traveling into the laboratory and moving about at the start of the procedure generally increased participants' core temperature levels, the first hour of each participant's data was discarded. The remaining 24 hours of temperature data was purified to remove the effects of sleep by two different methods.

The first was that developed by Carrier and Monk (1997) for protocols such as the current one, in which activity is restricted but sleep is permitted. The method applies an algorithm that differentially corrects temperature values recorded during sleep to account for the sleep-induced decrease in core temperature, which is most apparent in the first 60 minutes of sleep, then reduces through the rest of the sleep period. This is a particular strength compared to other methods that use a single correction factor for the entire sleep period.

The Carrier and Monk (1997) formula divides the temperature data collected during sleep into 10-minute bins and increases the raw temperature at each bin by a percentage of the range of temperature variation observed for the participant during their sleep period. For the first 6 temperature bins following lights out, the correction factor increases from zero by 9.1% of the temperature range. For each point following that
until waking, the correction factor is reduced by 1.1% of the temperature range. A weakness in the procedure is that it assumes that participants sleep continuously from lights-out until their morning waking, which is often not the case when people sleep in unfamiliar surroundings, and especially so in populations where sleep disorders may be present. To deal with the fact that a significant number of participants reported that it took some time to fall asleep, ‘lights out’ was operationalised as the time when significant movement ceased after retiring (as determined by the activity meter).

Despite these problems, visual inspection of corrected data profiles indicated that the method worked well at smoothing the sleep-induced temperature drop. The method was coded and applied using the statistical package SPSS (SPSS Inc. 1989-97), and corrected data were then submitted to non-linear regression using Cosifit, with frequency fixed at 1 cycle per day. This provided the summary parameters of mcsor, amplitude, phase and goodness of fit.

Purification by intercepts (Waterhouse et al., 1999) was applied to the temperature data as an alternative method of demasking the endogenous component of the rhythm. The major reason for also applying this method was the fact that it had led to the finding of significant differences between CFS and healthy participants in the strength of the relationship between core temperature and sleep-wake rhythms in the Study 2. As one of the objectives of the current study was to attempt a replication of the findings of Study 2, it was reasonable to use the same purification method. A second reason, however, for applying purification by intercepts was that, although it only used one
correction factor for sleep, movement associated with wakings during the night enables
correction of temperature data, although only if significant changes in core temperature
occurred at around that time. Although significant physical movement may not always
occur during waking periods, purification by intercepts may deal better with wakings
that are associated with activity, such as when the participant had to go to the toilet in
the middle of the sleep-period. In addition, the purification by intercepts method will
also correct for day-time movement associated with retiring, rising, and when it
significantly alters core temperature. As such, purification by intercepts is likely to
provide a more comprehensive demasking technique, even in controlled conditions, than
the method outlined by Carrier and Monk (1997).

Results

The parameters of mesor, amplitude, phase and the $r^2$ for the cosine fits for sleep activity
data, and phase and mesor for data coded to represent sleep-wake, were treated as
dependent measures in two separate MANOVAs, with group (Control vs CFS) as the
independent variable. A similar procedure was followed for the temperature rhythm
parameters, and MANOVAs were conducted upon the raw data, and upon that obtained
via each of the two purification methods. Means and standard deviations are
summarised in Table 7.1. As phase changes in the core temperature rhythm can occur
over the menstrual cycle (Liebenluft et al., 1995), and there were eight women in the
control group compared to four in the CFS group who were in the second half of their cycle, menstrual phase was tested as a covariate in the analyses of the temperature data. As it was found to be a significant covariate, it was included as such in all analyses involving temperature data. Depression (BDI) scores were significantly higher ($t(20)=4.56, p<.001$) in the CFS group ($M=15.00, SD=6.11$) than for controls ($M=6.05, SD=6.00$), and were subsequently tested as a covariate for all between group comparisons and used where it was found to significantly affect outcomes.

**Comparison of Sleep-activity Rhythms**

MANCOVA (with depression score as a covariate) found that sleep-activity patterns differed significantly between the two groups $F(4,32)=4.23, p<.01$ (See Table 7.1). Univariate ANCOVAs found that the CFS group had significantly lower activity mesor $F(1,35)=5.40, p<.05$, flatter amplitude $F(1,35)=3.981, p<.05$) and later acrophase $F(1,35)=8.50, p<.01$. This indicates that the CFS group was less active overall, that the difference between day and night in terms of their sleep-activity levels was less pronounced, and that they were phase delayed by approximately 1 hour.
Table 7.1
Means and standard deviations for sleep-activity, sleep-wake and core temperature (raw, purified by 16 category and purified by intercept methods) parameters for CFS and Healthy control groups.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Healthy Controls</th>
<th></th>
<th>CFS</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
<td>SD</td>
</tr>
<tr>
<td>Sleep-Activity Parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesor</td>
<td>.18</td>
<td>.30</td>
<td>-.22</td>
<td>.33</td>
</tr>
<tr>
<td>Phase</td>
<td>15:14</td>
<td>0:54</td>
<td>16:12</td>
<td>1:24</td>
</tr>
<tr>
<td>Amplitude</td>
<td>2.49</td>
<td>.31</td>
<td>2.36</td>
<td>.20</td>
</tr>
<tr>
<td>r-squared</td>
<td>.74</td>
<td>.06</td>
<td>.75</td>
<td>.06</td>
</tr>
<tr>
<td>Sleep-Wake Parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesor</td>
<td>7:26</td>
<td>0:53</td>
<td>8:00</td>
<td>0:62</td>
</tr>
<tr>
<td>Phase</td>
<td>3:25</td>
<td>0:36</td>
<td>4:28</td>
<td>1:29</td>
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<tr>
<td>Temperature Rhythm Parameters:</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Raw Data</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesor</td>
<td>37.02</td>
<td>.26</td>
<td>36.87</td>
<td>.23</td>
</tr>
<tr>
<td>Phase</td>
<td>16.54</td>
<td>1:35</td>
<td>17.58</td>
<td>1.35</td>
</tr>
<tr>
<td>Amplitude</td>
<td>.34</td>
<td>.13</td>
<td>.39</td>
<td>.17</td>
</tr>
<tr>
<td>r-squared</td>
<td>.86</td>
<td>.09</td>
<td>.83</td>
<td>.15</td>
</tr>
<tr>
<td>Data purified for Sleep</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesor</td>
<td>37.09</td>
<td>.26</td>
<td>36.97</td>
<td>.25</td>
</tr>
<tr>
<td>Phase</td>
<td>17.20</td>
<td>2:10</td>
<td>18.58</td>
<td>1.53</td>
</tr>
<tr>
<td>Amplitude</td>
<td>.25</td>
<td>.09</td>
<td>.25</td>
<td>.10</td>
</tr>
<tr>
<td>r-squared</td>
<td>.82</td>
<td>.08</td>
<td>.76</td>
<td>.12</td>
</tr>
<tr>
<td>Data purified by Intercepts</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesor</td>
<td>37.05</td>
<td>.30</td>
<td>36.89</td>
<td>.30</td>
</tr>
<tr>
<td>Phase</td>
<td>16.31</td>
<td>2:40</td>
<td>18.16</td>
<td>2:05</td>
</tr>
<tr>
<td>Amplitude</td>
<td>.29</td>
<td>.19</td>
<td>.31</td>
<td>.15</td>
</tr>
<tr>
<td>r-squared</td>
<td>.68</td>
<td>.24</td>
<td>.71</td>
<td>.26</td>
</tr>
</tbody>
</table>

Time between sleep and temperature acrophases when temperature data was:

|                          |       |       |      |          |
| Raw                       | 16:53 | 1:35  | 17.58| 1:35     |
| Purified for sleep        | 17:20 | 2:10  | 18.58| 1:53     |
| Purified by Intercepts    | 13.05 | 2:20  | 13.46| 1:39     |

*p<.05; **p<.01; ***p<.001.
Comparison of Sleep Timing and Amount

MANOVA also found significant differences between groups for sleep parameters $F(2,34)=5.76$, $p<.05$, with the CFS group having a later sleep acrophase $F(1,35)=11.31$, $p<.005$. Although CFS participants tended towards sleeping half an hour longer per day than controls, the difference was not significant $F(1,35)=0.289$, $p>.05$ ($p=.09$). In line with the sleep-activity rhythm as a whole, CFS sufferers’ sleep-phase was delayed by approximately 1 hour. It is noteworthy that, as well as being phase delayed compared to controls, the sleep acrophase of the CFS group was also significantly more variable ($SD=89$ minutes) compared to controls ($SD=36$ minutes), $F(18,18)=2.47$, $p<.05$ (see Table 7.1).

Comparison of Core Temperature Rhythms

MANCOVAs (menstrual phase as a covariate) with respect to rhythm parameters for core temperature also found significant differences between the groups for raw data $F(4,32)=3.47$, $p<.05$, data corrected for sleep $F(4,32)=3.32$, $p<.05$ and data purified by the intercepts method $F(4,32)=3.06$, $p<.05$. In all three cases, the only parameter that differed significantly between groups was temperature acrophase, with the CFS group demonstrating a phase delay. For raw temperature data, the delay was approximately 1 hour, $F(1,35)=8.30$, $p<.01$, for data corrected for sleep, it was closer to 1.5 hours,
F(1,35)=9.62, p<.005, and for data purified by intercepts, the calculated delay was approximately 1.7 hours F(1,35)=8.77, p<.005 (see Table 7.1).

Comparison of the Timing of Temperature Rhythms Relative to Sleep

As well as being tested for their phasc positions relative to the external environment, the timing of sleep and temperature was tested to assess their phase positions relative to each other. The time difference between sleep and temperature acrophascs for each participant was calculated by subtracting sleep acrophase from temperature acrophase when temperature data were raw and purified for sleep and by intercepts. Group means and standard deviations are shown at the bottom of Table 7.1. The time differentials calculated for each group (IV) by each method (DVs) were tested for overall difference via MANCOVA (with menstrual phase as the covariate). A significant overall effect was detected F(3,33)=3.06, p<.05. Follow up ANCOVAs found that the time difference between sleep and temperature acrophascs was significantly greater in the CFS group when temperature data were raw F(1,35)=8.26, p<.01 or purified for sleep F(1,35)=9.61, p<.01. The difference when data were purified by intercepts failed to attain significance F(1,35)=2.95, p>.05 (.09) (see Table 7.1). A greater difference between the acrophase of the core temperature rhythm and that of sleep indicates that, in the CFS group, core temperature rhythms were phase delayed relative to sleep.
Figure 7.1: Scatterplots of the relationships between the acrophases of core temperature and sleep-activity rhythms for each individual for raw core temperature data (A), core temperature purified using the Carrier & Monk (1995) purification for sleep (B) and that purified by intercepts Waterhouse et al. (1999) (C).
Consistency of the Relationship Between Sleep-wake and Core Temperature Rhythms

Consistency of the relationship between the internal pacemaker and the sleep-wake cycle was assessed by correlating sleep and temperature acrophase for each group. Analyses were conducted using core temperature acrophases calculated from raw data, as well as that correlated for sleep and purified by intercepts. Scatterplots are presented in Figure 7.1.

Correlations were calculated with the effects of menstrual phase partialled out. As outlined above, sleep acrophase in the CFS group was significantly more variable than for controls, and this is clear by visual inspection of Figure 7.1. As increased variability leads to an increase in the size of the correlation coefficient (Glass & Hopkins, 1996), direct comparison of coefficients between CFS and control groups is likely to underestimate the true difference in the relationships between sleep and temperature rhythms. Table 7.2, therefore, not only presents the coefficients calculated in the normal way, but also healthy control correlations corrected to match the increased variability in sleep acrophase of the CFS group (Glass & Hopkins, 1996).

Examination of Table 7.2 shows that correlation coefficients between sleep and temperature acrophase, when temperature is demasked, are lower for the CFS group, particularly when restricted variability of control sleep acrophase is adjusted for. Fisher’s Z (Howell, 1982), applied to test whether the significance of the differences
between CFS and control coefficients, found a significant difference between coefficients calculated from data purified by intercepts ($Z = 2.24$, $p < .05$), but not for raw data ($Z = 1.03$) or data corrected only for sleep ($Z = 1.36$).

Table 7.2.

Correlations between sleep and temperature acrophases for CFS and Control groups. Effects of depression (BDI score) have been partialled out. Coefficients corrected for relatively restricted variability of healthy control sleep acrophases are also presented.

<table>
<thead>
<tr>
<th></th>
<th>Correlation between sleep and temperature acrophases</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unpurified</td>
</tr>
<tr>
<td>Healthy</td>
<td>.63 **</td>
</tr>
<tr>
<td>CFS</td>
<td>.66 **</td>
</tr>
<tr>
<td>Adjusted Healthy *</td>
<td>.82 ***</td>
</tr>
</tbody>
</table>

*Correlations adjusted to account for significantly greater variance in sleep acrophase in CFS group.

$p < .05$; **$p < .01$; ***$p < .001$.

Relationship of Sleep and Temperature Rhythm Data with Symptom Measures

In order to explore the possible relationship between circadian functioning and CFS symptomatology, correlations between sleep and temperature parameters and symptom measures were calculated for both groups. The symptom measures tested were the
Somatic Symptom subscale from the MMPI (Lachar & Wrobcl, 1979), and the Vigour, Fatigue and Confusion subscales from the POMS (McNair et al., 1981). Coefficients involving temperature data were calculated with the effects of menstrual phase partialled out, and those presented in Table 7.3 were obtained using temperature data purified by intercepts, as this was the method by which the significant differences between Control and CFS groups had been found with respect to the relationship between sleep-wake and core temperature in the current and previous study. However, coefficients that were also significant when the Carriccr and Monk (1997) method was used are underlined.

In the CFS group, a higher sleep mesor was negatively associated with the number of somatic symptoms reported on the MMPI-2. This indicates that increased sleep was associated with fewer physical symptoms. The trend for fewer somatic symptoms to be associated with later sleep phase in the CFS group just failed to attain significance (p=.06). No other correlations between sleep and symptom measures were apparent for either group. In the CFS group, reduced amplitude and goodness of fit of the core temperature rhythm was associated with increases in the number of somatic symptoms reported and scores on the POMS Fatigue sub-scale. It should be pointed out that, in the CFS group, reduced temperature amplitude was highly correlated with its goodness of fit $r = .72$, $p < .001$. This was not so for the control group; $r = .20$, $p > .05$. 
Table 7.3.

Correlations of sleep-wake and temperature parameters with MMPI-2 Somatic Symptom Sub-scale and POMS Vigour, Fatigue and Confusion Sub-scales.

Correlations involving temperature have the effect of menstrual phase partialled out.

<table>
<thead>
<tr>
<th></th>
<th>MMPI-2 Somatic</th>
<th>POMS</th>
<th>POMS</th>
<th>POMS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>symptom sub-scale</td>
<td>Vigour sub-scale</td>
<td>Fatigue sub-scale</td>
<td>Confusion sub-scale</td>
</tr>
<tr>
<td></td>
<td>Healthy</td>
<td>CFS</td>
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<td>CFS</td>
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<tr>
<td><strong>Sleep-wake</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesor</td>
<td>.32</td>
<td>-.55*</td>
<td>.30</td>
<td>-.09</td>
</tr>
<tr>
<td>Phase</td>
<td>-.12</td>
<td>-.44</td>
<td>.00</td>
<td>.29</td>
</tr>
<tr>
<td><strong>Temperature</strong></td>
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<tr>
<td>Mesor</td>
<td>.20</td>
<td>-.12</td>
<td>.50*</td>
<td>.47*</td>
</tr>
<tr>
<td>Phase</td>
<td>.16</td>
<td>-.25</td>
<td>-.40</td>
<td>.62**</td>
</tr>
<tr>
<td>Amp</td>
<td>-.01</td>
<td>-.54*</td>
<td>.12</td>
<td>.33</td>
</tr>
<tr>
<td>$r^2$</td>
<td>-.10</td>
<td>-.51*</td>
<td>-.38</td>
<td>.34</td>
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<tr>
<td><strong>Sleep-Temp Difference</strong></td>
<td>.25</td>
<td>-.09</td>
<td>.48*</td>
<td>.43</td>
</tr>
</tbody>
</table>

* $p<.05$; ** $p<.01$; *** $p<.001$.

Coefficients involving temperature data entail that purified by intercepts. Underlining indicates that coefficients were also significant when temperature data were purified using the alternative method, correcting for sleep.

While reduced vigour was associated with increases in the core temperature mesor in control participants, the opposite was the case in the CFS group. However, the positive correlation in the CFS group was due mainly to the presence of two outlying scores on the POMS Vigour subscale, and when calculated without these cases, the coefficient
Figure 7.2. Scatterplots of POMS subscale scores against the timing of the core temperature acrophase, using data purified by intercepts (Waterhouse et al., 1999).
changed from +0.47 to -0.12. A strong trend for the groups to demonstrate opposite relationships between the symptom scales and the phase of the core temperature rhythm was also apparent. For the CFS group, later temperature phases were significantly associated with increased vigour and reduced confusion scores, while an association with reduced fatigue just failed to attain significance (p=.06). Again, however, the coefficient for the relationship between vigour and core temperature phase was substantially altered by the removal of the two significant outliers, from 0.62 to a non-significant 0.30. Later temperature phases in the control group were associated with increased confusion scores and a trend towards reduced vigour. Similarly contrasting trends were observed when temperature phase was measured relative to sleep, although significance was achieved only for the relationships between later temperature phase and reduced vigour and increased confusion in controls. Scatterplots are provided for these contrasting trends in Figure 7.2.

**Discussion**

As was the case in Studies 1 and 2, the sleep-activity rhythms of CFS participants compared to controls were characterised by lower overall activity levels and reduced amplitude. CFS sleep-activity rhythms were also phase delayed by just over an hour relative to controls, a finding which is consistent with the results of Study 1, but was not
replicated in Study 2. For CFS participants, the sleep phase itself was also delayed by just over an hour, however its timing was significantly more variable compared with controls. Similar to both previous studies, a non-significant trend towards CFS participants sleeping just over half an hour more per day than controls was observed. Core temperature rhythms differed between groups only with respect to timing, with significant phase delays found for the CFS group whether data were raw, corrected for sleep, or purified by intercepts. As was the case with the sleep-activity rhythm, raw data were phase delayed by an hour, although the purified temperature data suggested the delay was actually longer, between one and a half and one and three quarter hours. The longer delay in purified temperature rhythms meant that the phase position of core temperature rhythms was altered (delayed) relative to sleep as well as objective time. These findings are in contrast with those of Study 2, in which there was no significant between group difference in the timing of core temperature rhythms; in fact there was a trend towards a phase advance.

As was the case in Study 2, the relationships between the timing of sleep-wake and purified core temperature rhythms were poorer in CFS sufferers, and significantly so when the method of purification by intercepts was used. While the timing of sleep-acrophase accounted for 48% of the variance of core temperature acrophase in healthy subjects, the corresponding figure for the CFS group was only 27%. As has been noted, the significantly increased variability in sleep-acrophase that was seen in the CFS group means that these figures are likely to underestimate the relative differences between the
groups in this respect. When the control coefficient is calculated to adjust for the greater variability in the CFS group, the amount of variance accounted for in controls would be 68%, which is 2.5 times the CFS figure.

The replication of a number of the findings from Study 2 is encouraging, particularly since those results were obtained with a substantially larger patient group tested under tightly controlled conditions. Importantly, the replication was achieved using the same purification method that produced significant results in the earlier experiment. The fact that activity levels were held equal for both groups in the current study suggests that the original finding was not an artefact produced by an interaction between aspects of the purification method and systematic between-group differences in activity levels. This had been suggested to be the case with the alternative method, Purification by 16 Categories (Waterhouse et al., 1999), used in Study 2 (see: Discussion, Study 2). While the method of correcting temperature data for sleep (Carrier & Monk, 1997), did not result in significant differences in the sleep-temperature correlation coefficients, the trends were similar to those found when data were purified by intercepts. Although this method (ie correction for sleep) was one of those suggested to be unreliable by Klerman et al. (1999), the current protocol was more similar to the original validation study (Carrier & Monk, 1997) than the Klerman et al. (1999) study was, in that physical activity was largely eliminated as a nuisance variable, as the designers of the protocol intended (Carrier & Monk, 1997). The fact that the Carrier and Monk (1997) correction for sleep method did not result in as large a difference between groups as the
Waterhouse et al. (1999) purification by intercepts method did may have been due to the previously raised issues of sleep-discontinuity and the fact that participants were not completely sedentary. As such, the purification by intercepts method (Waterhouse et al., 1999) may be superior, even when physical activity is restricted. It is possible, also, that temperature increases associated with food intake were incidentally controlled for by the purification by intercepts technique, in that such rises, where significant, might be associated with the small increases in physical movement that often occurred around meal times (participants often sat up, went to the toilet before or after eating etc.). Thus, even though the method might be erroneously attributing the rise to increased movement, rather than thermogenesis resulting from increased metabolic activity related to nutrient intake, the correction applied could nevertheless improve demasking. In any case, it is difficult to see how the significant between-group differences found via the use of the purification by intercepts technique in the two methodologically distinct studies could be due a procedural artefact.

One of the major theories being investigated in this thesis is that reduced activity levels, flatter amplitude of the sleep-activity rhythm and greater variability in the timing of the nocturnal sleep phase may mean that the lifestyle of people suffering from CFS is likely to offer the circadian system fewer cues with which to synchronise itself and the rhythms that depend upon it. Given the nature of the illness, and the common need for daytime rest or sleep periods, it is also suggested that the light-dark cycle to which CFS sufferers are exposed is likely to be less salient than that available to healthy individuals.
The findings of the three studies presented so far, which have consistently indicated that reduced activity levels and reduced amplitude of the sleep-wake rhythm are indeed associated with CFS, provide a strong indication that the sleep-activity patterns of many CFS sufferers are likely to offer the circadian system fewer or less salient time cues with which to externally synchronise.

While it is not possible to know whether this reduction was substantial enough to affect the functioning of the circadian system, the significant phase delay of the core temperature rhythm suggests that it may have been. As has been outlined in earlier chapters, the fact that the natural period of the human circadian clock is slightly longer than 24 hours means that there is a tendency for physiological and, subsequently, sleep-wake rhythms to progressively phase delay (Wever, 1986). The fact that the delay in core temperature found in CFS participants was longer than the delay in sleep-wake suggests that sleep-wake rhythms were being ‘dragged’ later in the CFS group by physiological rhythms that were consistently delayed, perhaps because there were too few external cues to efficiently curtail their natural period. The results of Study 1, in which sleep-onset and waking times were delayed in spite of normal, and consistent bedtimes, provides further support for this hypothesis.

The scenario suggested by these data is one that is somewhat similar to that of delayed sleep-phase syndrome (DSPS), in which a degree of struggle exists within the circadian system of the individual in whom the need to maintain a normal social rhythm competes
with the natural tendency to follow their internal clock. The causes of DSPS have been posited to be related to behavioural factors, such as late and irregular sleep patterns, and physiological factors, such as longer periods of the endogenous pacemaker and/or weaker entrainment mechanisms (Morris et al., 1990; Ozaki et al., 1988). Although the delay in temperature and sleep timing of the CFS group in the current study is by no means as substantial as that usually associated with DSPS, the internal ‘struggle’ between physiological and social rhythms may nevertheless contribute to the greater inter-individual variation in sleep-timing in CFS, as well as the apparent reduction in the strength of entrainment between sleep-wake and core-temperature rhythms.

The exploratory analyses investigating the relationships between rhythm parameters and symptom measures offered interesting, although somewhat perplexing, findings. Of course, correlation implies nothing about causation and, as such, suggestions as to the underlying nature of relationships found between the variables tested is purely hypothetical and can only be verified by further research. For instance, the finding that increased sleep was associated with fewer reported somatic symptoms in the CFS group may indicate either that sleep limits symptomatology or that symptomatology limits sleep. A further possibility is that the relationship is spurious, and that the underlying dysfunction(s) that produce increased somatic symptoms also led to less sleep.

The significant positive correlations between the symptom variables (number of somatic symptoms and fatigue) with core temperature amplitude (and with goodness of fit to a
cosine function with a 24 hour period) are, perhaps, the most interesting. They suggest a link between symptomatology and physiological functioning, and are, to some degree, consistent with the findings of other recent work (MaclHale et al., 1998). Due to the fact that these two temperature parameters were strongly correlated in the CFS group, it is uncertain as to which, if indeed either, is more important in its relationship with the symptom variables. Both measures may reflect a general reduction of the salience in the core temperature rhythm or, indeed, the salience of rhythmic output from the SCN in CFS, and that this is the crucial factor.

A problem with this conclusion is, however, that the core temperature rhythm amplitudes of the CFS group in the current study were not reduced overall compared to controls. In part, this may be due to the fact that more women in the control group were in the luteal phase of the menstrual cycle, which is associated with flatter amplitude and later phase of the core temperature rhythm (Liebeluf et al., 1995). Covarying for the differences may not have succeeded completely in accounting for the effect. A previous study (Hamilos et al., 1998) reported significantly lower amplitude and poorer fit of the core temperature rhythm in a small group of CFS sufferers, although it appears that the effects of activity and/or sleep were not controlled for. In contrast, a study with a similar number of participants to the current investigation, in which the effects of sleep and activity were controlled for, found no difference in temperature amplitude between CFS and healthy participants (Williams et al., 1996). In Study 2, where people were studied in their normal environments, neither core temperature amplitude nor goodness
of fit were significantly different in CFS and healthy participants, although both showed a tendency to be lower in the CFS group.

Studies of other physiological parameters in CFS have indicated that alterations in rhythm amplitudes may occur. Van de Luit et al. (1998) found significantly increased amplitudes of systolic and diastolic blood pressure and heart rate in their group of 18 CFS sufferers compared to 12 age- and sex-matched controls. MacHale et al. (1998) reported finding a significant reduction in the diurnal variation of cortisol levels and that this was significantly related with some measures of functional status. As noted in Chapter 4 of this thesis, however, the methodology employed in this study meant that the reported reduction in diurnal variation of cortisol could be confounded by systematic differences between groups with respect to phase.

While the steady-state phase and period length of physiological variables under non-entrained conditions are viewed as parameters directly representative of the endogenous pacemaker, amplitude can be influenced to a large extent by factors downstream from the clock itself (Turek, 1994). It is therefore possible that the relationship found here between temperature amplitude and symptomatology is spurious, or that some other factor or factors that are responsible for increases in symptom number and/or severity are sensitive to changes in temperature amplitude. While the amplitude of the endogenous temperature rhythm might be unaltered in CFS sufferers, exogenous and/or pathological factors that affect its expression may lead to an exacerbation of symptoms.
One such factor could be the demonstrated desynchrony between sleep-wake and core temperature rhythms. This could lead to a reduction in temperature amplitude in that, rather than enhancing the endogenously produced cyclic rises and falls in temperature, sleep-evoked decreases and activity-evoked increases would be, to some degree, opposing them. Reduced activity levels through the day, and sleep disturbance at night, would further impact upon core temperature amplitude. This scenario could provide at least a partial explanation of the current findings of a significant relationship between core temperature amplitude and symptom measures, even though there was no difference between CFS and controls with respect to core temperature amplitude itself.

The paradox entailed in the reversed relationships between other symptom measures and temperature parameters in CFS and control groups are more difficult to account for. Even though the reversed relationship between core temperature mesor and vigour can be attributed almost entirely to an outlier effect, outliers were not responsible for the reversed relationships, or trends towards such, for core temperature phase and symptom measures. In isolation, it is possible to explain the finding that, in controls, later temperature acrophase, especially when measured relative to the sleep period, was related to reduced vigour and increased confusion. Firstly, this is because it is reasonable to expect that, as the temperature rhythm becomes more out of phase with sleep-wake, general well-being is likely to decrease. Secondly, the CFS group, who rated more poorly on these measures due to the nature of their illness, also demonstrated significant phase delays in their temperature rhythms.
The conundrum, therefore, is in explaining the finding that the temperature delay was actually related to improved functioning in the CFS group. As was noted earlier, previous research has indicated that sleep occurring on the rising limb of the core temperature rhythm is more disturbed (Dijk & Czeisler, 1995), and that delays in sleep relative to the core temperature rhythm are associated both with disturbances to sleep and affective functioning, even in healthy individuals (Surrige et al., 1986). A delay in the core temperature rhythm relative to sleep, as was found with the current CFS group, would mean that sleep was less likely to occur at such a time and may, therefore, have the effect of increasing the overall quality of sleep, especially late in the sleep period. Although delayed temperature rhythms presumably also have some negative impact, as appeared to be the case for controls, this may thus be outweighed in CFS patients to some extent. Such explanations are, however, necessarily tenuous given the exploratory nature of this aspect of the study and the need for these findings to be repeated and elaborated upon by future work.

Overall, the results of this study provide further evidence to support the hypothesis that behavioural and physiological circadian functioning is altered in CFS patients. While phase delays in sleep and temperature rhythms were clearly apparent, increased variability of the timing of sleep and a weaker relationship between sleep and temperature rhythms indicates that the circadian time-keeping system of CFS sufferers is dysregulated to some extent. The source of this dysregulation is unclear. Although the reductions in sleep-activity rhythm messor and amplitude that have been demonstrated in
CFS patients in the three studies conducted to date raise the possibility that a lack of behavioural time cues may make it more difficult for the system to entrain efficiently, it could equally be argued that the dampening of behavioural rhythms is a result of physiological dysregulation. The importance of circadian dysregulation in CFS is also unknown, as the findings of associations between rhythm parameters and symptom variables do not reveal the nature of the causal relationship.

In order to answer these questions, it is necessary to examine the effects of improving the salience of environmental and behavioural time cues with the aim of improving circadian integrity. Any improvement in symptoms following such an intervention would suggest, firstly, that circadian dysregulation was produced, at least to some extent, by lifestyle factors and, secondly, that circadian dysregulation played a causal or maintenance role in the symptomatology of CFS. A lack of change in the symptomatology of sufferers following such interventions would suggest that either or both of the above conclusions were wrong. Such an intervention may not produce improvements in the symptoms of CFS either because circadian dysregulation is an epiphenomenon of CFS; or, because the dysregulation is not a result of lifestyle factors and, therefore, is not affected by lifestyle changes: or, circadian dysregulation neither results from lifestyle alterations nor contributes to symptomatology.

Interventions should primarily be directed at regularising and consolidating patterns of sleep-wake and their phase relationship with the endogenous pacemaker, while they also
seek to improve the amplitude of the sleep-activity rhythm. Resynchronisation could be achieved by implementing regular patterns of sleep and wake, coupled with the use of appropriately timed exposure to bright light. Amplitude of the sleep-activity rhythm could be improved by interventions designed to consolidate the nocturnal sleep period, and encourage tolerable activity levels through the day.

The focus of this thesis will now, therefore, move to addressing the fourth and final aim outlined at the end of Chapter 4, which was to investigate the clinical significance of circadian dysregulation in CFS.
CHAPTER 8

STUDY 4: A PRELIMINARY PLACEBO-CONTROLLED TRIAL OF CLINICAL INTERVENTIONS DESIGNED TO RESTORE CIRCADIAN INTEGRITY IN CHRONIC FATIGUE SYNDROME
Introduction

The first three studies of this thesis have provided evidence of circadian dysregulation in the behaviour and physiology of CFS patients. Behavioural dysregulation has appeared mainly in the form of increased variability in the timing of sleep, reduced amplitude and mesor of the sleep-activity rhythm, and a general phase delay of sleep–activity cycles relative to the ambient light-dark and social rhythms of the environment. Phase delays were also found for the core temperature rhythm, suggesting that the delay in sleep-activity was indicative of a general phase delay of the entire circadian system. Most prominently, the relationship between the sleep-wake and the core temperature rhythm was found to have been significantly weaker in CFS sufferers compared to healthy individuals, and this provided perhaps the strongest indication of generalised circadian dysregulation in CFS. The delays in behavioural and physiological cycles, and the relative lack of association between sleep-wake and core temperature rhythms is evidence that the group of CFS patients examined in these three studies demonstrated both external and internal circadian desynchrony.

Although such disturbances could, in theory, contribute to the onset and maintenance of the symptom complex, their actual clinical significance cannot be deduced from the studies carried out so far. The relationships observed in Study 3, between core
temperature rhythm parameters and symptom variables, provided evidence that circadian
dysregulation and CFS symptomatology are linked in some way. The significant
negative association between the magnitude of the diurnal change in plasma cortisol
levels and measures of disability reported by MacHalc et al. (1998) provide further
evidence of a connection. However, as has been pointed out in Study 3 the nature of the
link remains unclear. In order to establish whether circadian dysregulation contributes
to the symptoms of CFS, intervention studies are required in which the degree of
circadian dysregulation is manipulated while symptoms are monitored for any changes
that might take place. The most obvious way to manipulate the level of circadian
dysregulation would be to attempt to reduce it via clinical intervention. The impact, or
lack thereof, upon the symptoms of CFS of interventions specifically aimed at restoring
or improving the integrity of the circadian system, would provide a strong indication of
the significance of circadian factors in the illness.

Clearly, the fundamental goal of such an intervention would be to restore and maintain
external and internal circadian synchrony. Given that, as a group, CFS participants
exhibited a phase delay in circadian functioning, the restoration of external synchrony
would require an advance of sleep-activity and physiological rhythms. To some degree,
such a measure is contraindicated by the results of Study 3, in which phase delays were
correlated with fewer symptoms in the CFS group. Nevertheless, restoration and
maintenance of synchrony between sleep-wake patterns and the prevailing social and
environmental cycle is likely to be important for several reasons. Firstly, one's sleep is
less likely to be interrupted by external stimuli when it fits with the general sleep-activity pattern of the social environment. Secondly, sleeping through the dark phase, and being active through the light, is also likely to increase the opportunities for exposure to a salient light-dark cycle. Thirdly, being in synchrony with the social patterns of one’s environment is likely to increase one’s opportunities to engage in various social and physical activities through the day and to reduce social isolation. Finally, in contrast to the CFS group in Study 3, control data indicated that phase delays were associated with increases in symptomatology, supporting the contention that, fundamentally, a delay in sleep-activity rhythms is not conducive to healthy functioning.

As has been discussed elsewhere in this thesis (Chapter 4), external desynchrony in itself is not an intrinsically unhealthy state. The negative health consequences associated with conditions in which external desynchrony is the major feature, such as jet lag, shiftwork, and delayed sleep phase syndromes, are more directly related to the internal circadian disorganisation that is engendered as a result of the mismatch between environmental and internal time cues and the fact that some rhythms take longer to adjust than others (Arendt, 1998a; Armstrong, 1991). As such, restoration of external synchrony would be a first, important step in the restoration of internal synchrony. In theory, it should be the only necessary step, in that, provided that physiological and behavioural rhythms are properly entrained to the external environment, internal synchrony should ensue. Once achieved, external synchrony would have to be maintained over a significant period of time, firstly to allow for the fact that
physiological rhythms resynchronise more slowly than behavioural rhythms (Armstrong, 1991), and second, to allow any of the potential health benefits of restored circadian integrity to occur.

Properly timed exposure to light of appropriate wavelength, intensity and duration has been established as the most effective means for resetting the timing of the biological clock in humans (Czeisler, 1995; Duffy, Kronauer & Czeisler, 1996; Morita & Tokura, 1998). The mechanisms by which light is able to produce alterations in the timing of the SCN rhythm are the same as those that enable entrainment of the human circadian system to the ambient light-dark cycle, which were outlined in detail in Chapter 4. As is the case in other mammals, the human system is particularly responsive to light of mid-short wavelength, such as that with a high colour temperature and green and blue light (Morita & Tokura, 1998). Light of long wavelengths, such as that with a low colour temperature and red light, has little effect on circadian timing (Morita & Tokura, 1998). Typically, where acute phase shifts of the human clock are required for clinical and/or research purposes, full spectrum light of between 2,500 and 10,000 lux has been employed, for durations that have varied from 15 minutes to 5 hours, with longer exposures generally leading to greater shifts (Czeisler et al., 1986; Drennan, Kripke & Gillen, 1991; Lack & Wright, 1993; Minors, Waterhouse & Wirz-Justice, 1991; Rosenthal et al., 1990; Terman et al., 1995). Most studies entail exposure sessions conducted over three or more consecutive circadian cycles, however, several studies indicate that significant phase shifts can be achieved after a single exposure session of
sufficient intensity and duration (Dawson, Lack & Morris 1993; Honma, Honma & Wada, 1987; Minors et al., 1991). Even so, maintenance of the phase shift often requires continued treatments, especially in patients whose circadian systems demonstrate a pathological tendency to delay or advance relative to the ambient 24-hour cycle (Terman et al., 1995).

The largest phase shifts in the SCN rhythm are achieved when light exposure is timed to be close to the minimum of the core temperature rhythm which, in humans, generally occurs in the middle to late part of the nocturnal sleep period (Czeisler, 1995). Minors et al. (1991) showed that single, three-hour pulses of full spectrum light (5000-9000 lux) were able to produce phase shifts of the core temperature rhythm of up to two hours. Maximal phase delays were achieved when the light pulse was delivered immediately prior to the nocturnal minimum of the core temperature rhythm, while pulses delivered immediately following the temperature minimum led to maximal phase advances. The phase altering impact of the light pulses diminished as their temporal proximity to the core temperature minimum decreased, with those occurring more than 6 hours either side having little effect (Minors et al., 1991).

For the sake of convenience, light exposure in clinical practice is usually conducted immediately before bedtime, or upon awakening, depending on the desired direction of the phase shift. Although this practice can be problematic in cases where the SCN rhythm is significantly out of phase with the sleep-wake cycle, it is generally adequate,
provided that close monitoring of sleep-wake patterns is carried out for several weeks upon the initiation of the exposure program in order to detect and adjust for unwanted shifts or lack of treatment effect (Terman et al., 1995). Bright light treatment has been used to good effect in the treatment of disturbances of sleep-phase and duration (Czeisler, 1995; Lack & Wright, 1993; Rosenthal et al., 1990; Terman et al., 1995), sleep-maintenance insomnia (Campbell, Dawson & Anderson, 1993) maladaptation to shift-work (Czeisler et al., 1990; Eastman et al., 1995, Van Reeth, 1998) and jet-lag (Boulos et al., 1995).

Although strenuous nocturnal activity is able to produce significant phase-shifts in humans (Buxton et al., 1997a &b; Van Reeth et al., 1994), its general use in patients suffering from CFS is untenable for obvious reasons. Other non-photic cues, such as the timing of the sleep-wake cycle itself, normal sedentary activity and social interaction have relatively little impact in resetting circadian timing (Duffy, Kronauer & Czeisler, 1996; Honma et al., 1995), although it has been known for some time that they are enough to maintain entrainment to a 24-hour day, when lighting conditions are held constant (Aschoff, Fatranska & Giedke, 1971). As has been suggested several times in previous chapters, a lack of non-photic cues, combined with inadequate exposure to a salient light-dark cycle may be a major contributing factor to the general phase delays demonstrated by CFS patients in two of the previous three studies. The lower activity levels and reduced sleep-activity amplitude demonstrated by CFS groups in all three
studies suggests that non-photic cues are likely to be weaker in people suffering from the disorder.

Interventions that seek to address these deficits, by assisting patients to regularise sleep-wake schedules, increase daytime levels of physical activity and social interaction, and consolidate and improve the quality of the nocturnal sleep period could, therefore, augment the resynchronising effects of appropriate light treatment as well as improve the chances of maintaining internal and external synchrony, presuming it is achieved. Such an intervention would require the development of appropriate behavioural goals and strategies aimed at their attainment, education about issues such as circadian rhythmicity, healthy sleep behaviour and the impact of physical activity in CFS, and general support and problem solving with regard to issues that arise in the course of implementing the behavioural program. Given its emphasis on goal setting, adaptive learning and problem solving, all within a time-limited context, a cognitive-behavioural framework (Hawton, Salkovskis, Kirk & Clark, 1993) would seem to be an appropriate method of delivery of such an intervention. As was discussed at the end of Chapter 3, CFS is a complex, multifactorial condition that is extremely unlikely to be understood or treated successfully via a unidimensional approach. The multidimensionality offered by cognitive-behaviour therapy (CBT), and the fact that it operates well within a biosocial framework, are features that are likely to have contributed to its relative success as a treatment for CFS compared to more unitary approaches (Deale et al, 1997; Sharpe et al., 1996).
The aim of the following study was to conduct a controlled evaluation of the effects of interventions designed to restore and maintain both external and internal circadian synchrony in people with CFS. The major intervention tested was a program of appropriately timed exposure to full-spectrum light of greater than 2,500 lux, combined with 7 sessions of cognitive-behaviour therapy, aimed primarily at increasing the salience of the sleep-activity cycle as a non-photic zeitgeber for the circadian system. While one group of patients were offered the full program of CBT and bright light exposure, two further groups were offered either the bright light component or the CBT component in isolation. This aspect of the design was implemented in order to assess the relative impact of each of these treatment components. Finally, the efficacy of these three therapeutic programs was compared with that of a placebo condition, in which patients were put on a program of exposure to light of a wavelength and intensity known to have no significant impact on the circadian system.

Method

Participants

Participants were recruited and screened using the same procedures as in the previous studies. In total, 40 individuals (8 males and 32 females) meeting the CDC criteria for CFS (Fukuda et al., 1994) participated in this study. Participants ranged in age from 18
to 68 years (M=38.61; SD=11.82), and in illness duration from 1.5 to 32 years (M=6.47; SD=5.68). Two major conditions of participation were the acceptance of random allocation to treatment condition and that no new treatments be commenced, at least until the 8 week assessment and treatment process had been completed, and the immediate post-treatment assessment carried out. Those participants who were undergoing other forms of treatment, such as antidepressant and other pharmacological intervention, or various complimentary therapies, were accepted into the study provided that these interventions had been commenced at least 3 months prior to recruitment, and that no changes in symptoms had been experienced within that (3-month) period.

This study was commenced concurrently with Study 3. Participation in the treatment study was offered first to patients who had been involved in the earlier temperature monitoring studies. All 19 participants from Study 3 took up the offer, and their treatment was implemented immediately following the temperature monitoring procedure conducted for that study. Of the remaining 21 participants, 6 had been involved in the earlier temperature monitoring study (Study 2), 8 had been involved in Study 1, and 7 were newly recruited.
**Design**

A block randomisation procedure was used to allocate 10 participants to each of one of the four treatment conditions (N=40). A set of four cards was printed, each with the name of one of the treatment conditions. As participants were admitted to the study, each cohort of four was allocated to conditions by the drawing of these cards at random from a box. Participants allocated to Condition 1, cognitive–behavioural therapy plus light (CBT+Light), were offered a 7 session program (following 3 assessment sessions) run over 6 weeks that entailed regular sessions with a clinical psychologist, as well as a six-week program of regular, appropriately timed exposure to bright light. Those allocated to Condition 2, cognitive behaviour therapy plus placebo light (CBT+Placebo), were also provided with the regular sessions with the clinical psychologist, and a six-week light-exposure program. However, the light given was non-therapeutic with respect to both frequency and intensity (see below). Participants allocated to Condition 3, bright light therapy alone (Light) were given the six-week light exposure program only, while those allocated to Condition 4, placebo only (Placebo) were given the six-week non-therapeutic light exposure program. Patients in all conditions underwent three assessment sessions, conducted over three weeks. Interventions were carried out over 6 weeks.

As a part of the process of obtaining informed consent, participants were informed that participation in the study entailed the possibility that they would be allocated to a
placebo treatment condition. Immediately following the post-treatment assessment, the 10 participants who had been allocated to the Placebo group were debriefed. Debriefing included a (largely anecdotal) summary of the apparent effectiveness of the alternative programs. They were then offered up to 10 sessions of CBT and/or up to six weeks of bright light treatment. Seven participants took up the offer.

*Treatments*

The efficacy of two treatment modalities, cognitive-behaviour therapy (CBT) and regular, appropriately timed bright light exposure, were tested alone and in combination with each other. The rationale for testing these three different levels of intervention was to enable and assessment of the relative effectiveness of the two major treatment components entailed in the CBT+Light condition. A summary of each treatment condition is provided below. More detailed treatment protocols are provided in Appendices C, D and E.

*CBT Program*

The major focus of the behavioural part of the program was on the development of daily routines with respect to sleep and physical activity. Patients were encouraged to develop and implement a schedule of regular bed and waking times, and to work towards
appropriate increases in the amount and intensity of regular physical activity. General information on CFS was provided, and patients were assured that appropriately tailored increases in physical activity were likely to be beneficial and unlikely to produce relapses. The issue of sleep quality was addressed by examination of sleep diaries and sleep behaviour in general. Information on sleep hygiene and factors that may either promote or inhibit good sleep was provided and discussed with respect to how the patient might increase the overall quality of their sleep. The cognitive component was introduced while behavioural routines were being implemented. Sessions during this phase focused on identifying and challenging erroneous beliefs and attributions that feed avoidance of physical, mental and social activity. The general theme of this part of the project was to the effect that, while the causes and nature of CFS might remained poorly understood, and there was no 'cure' available, there were, nevertheless, some aspects of the syndrome which were controllable. The suggestion was made to patients that the impact of the illness could be reduced, at least to some extent, through the identification of, and appropriate attendance to, these areas.

**Light Exposure Program**

The program of regular exposure to bright light of appropriate intensity and timing entailed the development of a basic sleep-wake routine, and the implementation of a light exposure program designed to restore and/or maintain sleep-wake/SCN synchrony. The clinician worked with the patient to develop a reasonable routine of bed and rising times. As was also the case in the CBT program, this goal routine was developed with
the aim of achieving external synchrony, and so to match as closely as possible with the general patterns of the patient’s social environment (eg the rhythms of their partner, household or workplace). Where the goal routines were not substantially different from their current sleep-wake behaviour, patients were encouraged to adopt the routine immediately by sticking to a regular bed-time, setting their alarm for a regular wake-time, and carrying out daily light exposure sessions starting within a half hour of waking and lasting between 30 and 45 minutes. Where goal routines differed significantly from the patient’s sleep-wake habits at the time (this was always because of a phase delay of habitual sleep time relative to desired sleep time), a gradual phase advance of the sleep-wake rhythm was undertaken, accompanied by a number of 3-hour light exposure sessions. This process, which usually took 3 to 4 days, and never longer than a week, was designed to reset SCN and sleep-wake rhythms in line with the timing of the goal routine. At this point, the maintenance program was implemented. Throughout treatment, patients maintained a sleep diary, which was monitored by the clinician during regular appointments. Where appropriate, the light exposure protocol was altered to facilitate entrainment to the goal routine. Such alterations were necessary in cases where patients appeared to have phase advanced too far, or not enough.

Patients were provided with light boxes that emitted white light of 5000 lux intensity at 60cm distance. The light boxes used for the study are commercially produced and distributed (Outside In, UK), primarily for sufferers of Seasonal Affective Disorder. The use of the boxes was demonstrated to patients and progress was monitored via
sleep-diaries (Appendix F) that were reviewed at regular clinical sessions over the 6-week intervention period.

**Placebo Light Program**

The placebo light condition entailed the use of the same light boxes as for the bright light treatment, however a red filter was applied to the unit so that red light of less than 250 lux intensity was available at 60cm from the unit. Participants in this group were told to sit no closer than 60 cm and to conduct daily exposure for a half hour upon waking. Regular sleep and waking times were suggested to the patient by the clinician, but were not specifically discussed after the first treatment session. Sleep-diaries were maintained and progress was reviewed at regular appointments over the six-week period, as for the other treatment groups.

**Treatment Group Summary**

In the treatment trial, the CBT+Light condition simply entailed the combination of the CBT and Light treatment protocols outlined above, while the CBT+Placebo condition combined the CBT treatment and placebo light protocols. Those allocated to the Light condition received only the program of exposure to bright light, while those allocated to the Placebo condition received a program that was, fundamentally, the same as the Light condition, except that the light was sub-therapeutic.
Measures

Five general measures were used pre- and post- treatment to assess the relative efficacy of the four protocols. Below is a brief description of each instrument used, the meaning and ranges of scores for each scale are provided in the results section, where the relevant data appear.

1. Fatigue Assessment Inventory (FAI; Schwartz et al., 1993).

The developers of this scale have reported that it measures four separate dimensions of fatigue: Global Fatigue Severity; Situation-specific Fatigue (whether specific factors such as heat or stress are more likely to bring on fatigue); Fatigue Consequences (the impact of fatigue upon general functioning); and, Responsiveness (the extent to which fatigue is alleviated by rest or sleep). The instrument contains 29 items scored on a seven-point Likert scale, is of good psychometric quality, and is one of the instruments recommended for use in CFS research by the CDC (Fukuda et al., 1994). The primary aim of using the FAI was to assess the impact of treatment with respect to fatigue.
2. **The Profile of Mood States (POMS: McNair, Lorr & Droppelman, 1981).**

The POMS, which was described in detail in Chapter 7, has been widely used in treatment evaluations and has been recommended for use as a psychotherapy change measure (Little & Penman, 1989). The POMS was employed due to the fact that all but one of its subscales (anger-hostility) has direct relevance to the symptomatology of CFS and because of the associations found in Study 3 between POMS subscales (fatigue, confusion and vigour) and circadian functioning.

3. **Beck Depression Inventory-II (BDI: Beck & Steer, 1996).** As was the case for Studies 2 and 3, the BDI was used primarily as a way of assessing for the presence of depressive symptomatology so that the effects of depression could be controlled for where necessary in statistical analyses.

4. **Medical Outcomes Scale Short-Form 36 (SF-36: Ware & Sherbourne, 1992).**

The short-form of the Medical Outcomes Scale consists of 36 questions yielding an 8-scale health profile as well as summary measures of health-related quality of life. The SF-36 subscales used for the current study were: Physical Functioning; Bodily Pain; Role Impairment (Physical); Role Impairment (Emotional); Social Functioning; General Health Perceptions; and Health Change. The SF-36 meets or exceeds minimum standards of psychometric quality (Ware & Sherbourne) and has been used in over 200 internationally published studies as a method for assessing the impact of various treatment protocols (Manocchia, Bayliss & Conner, 1996). The
CDC also listed the SF-36 as among the preferred instruments for assessing the status of CFS sufferers in research programs (Fukuda et al., 1994). The primary aim of using the SF-36 was to assess the impact of treatments on general health and functioning.

5. *Sleep-Activity Logs*

The two-week sleep-activity diaries were employed to assess whether sleep-activity rhythms changed as a result of treatment, and to be able to measure any such changes against changes in symptomatology.

*Procedure*

After the initial assessment session, participants who met the CDC criteria were provided with the sleep-activity logs, which they then filled out over the subsequent two weeks. At the end of this two-week period, they were asked to fill out the FAI, BDI, POMS and SF-36 and, together with the log-book, these served as the baseline data set. Treatment was carried out over the ensuing 6-week period, and at the end of this time, participants were again asked to complete two weeks of sleep-activity monitoring and to fill out the five instruments. This provided the immediate post-treatment assessment. Participants were followed up again approximately six months from commencing treatment. The data relating to the 6-month follow-up assessment are reported in the next chapter.
Results

Compliance and Drop-out Rates

Three participants, two from the CBT+Light group, and one from the Light only condition, complained of discomfort related to the bright light exposure. The first of these reported increases headaches, dizziness and insomnia, the onset of which coincided with the commencement of the light exposure sessions. Light-exposure was ceased after two days, and the symptoms had resolved after another three. The participant did not feel comfortable about trying the light exposure again, although she was keen to continue with the CBT component, and completed this aspect of the treatment. The other two found the light intensity to be too high to be able to comfortably stand for more than a short time (minutes). In both cases, making adjustments to the conditions under which light exposure was carried out, and slightly increasing the distance from the light (2,500 lux threshold) was acceptable. One other participant, from the CBT+Placebo group, did not attend any appointments after the initial assessment sessions, stating that she felt too unwell to make the journey into the university clinic. She continued with the (placebo) light exposure program, and was sent the relevant information sheets by mail. Weekly telephone contact was made in place of missed appointments, but these generally only dealt with routine implementation and general health concerns.
No direct compliance measures were carried out, apart from session attendances. Although a number of appointments had to be rescheduled, most participants attended and completed all sessions, with the average attendance rate across conditions being 91.6%. All participants completed pre- and post- outcome surveys, and analyses were conducted on an intention to treat basis.

Analytic strategy

In order to reduce the Type I error rate experiment-wise, individual measures associated with the sleep-activity log, FAI, POMS, SF-36 and BDI were grouped a priori, according to the general aspect of outcome they assessed. Six general areas of outcome were tested, including: Sleep-Activity rhythms, General Fatigue, General Symptoms, General Impairment, General Health, and General Psychological Functioning (see Table 8.1).

Sleep activity rhythms were assessed using the logbook data. These were treated as previously, by applying non-linear least squares regression in order to obtain summary parameters of mesor, amplitude, phase and fit to a 24-hour period. These four parameters made up the first set of dependent variables (DV$s), which were used to assess for changes in the sleep-activity rhythm overall. The set of DV$s that were used to assess for general changes in fatigue incorporated the four subscales from the FAI, as well as the POMS Fatigue subscale. The general symptoms category incorporated the SF-36 scales for physical functioning and pain, and the POMS confusion scale. General
impairment was measured by SF-36 Role Impairment scales (Physical and Emotional), as well as the SF-36 Social Functioning scale. General Health was measured by SF-36 General Health Perceptions and Health Change Scales. Finally, General Psychological Functioning was assessed using BDI and POMS Depression and Anxiety Sub-scale scores.

Statistical analyses of changes in each of these DV sets between pre- and post-testing was conducted via doubly-multivariate repeated measures analysis of variance. Group (CBT+Light, CBT+Placebo, Light Only and Placebo Only) was tested as a between-subjects independent variable (IV) with Time (pre- and post-intervention) as the within-subjects IV. Significant group by time interactions, indicating that the nature of the change in DVs across time differed between groups, were followed by univariate group by time repeated measures ANOVAs on each of the dependent variables within the set. Significant group by time effects at this stage were then followed by repeated measures ANOVAs within each group to discern the nature of the interaction. In cases where no significant group by time interactions were present, significant main effects for time were followed by repeated measures ANOVAs, for each DV, in order to assess for time effects after collapsing across groups. Significant main effects for group were followed by univariate ANOVAs to determine overall group differences on the DVs, and post hoc comparisons (Tukey’s HSD) in order to assess where group differences occurred. All data were screened prior to analysis for normality, linearity and homoscedasticity, with
Table 8.1.

Grouping of dependent variables into sets representing general categories of outcome assessed statistically via doubly-multivariate repeated measures MANOVAs.

<table>
<thead>
<tr>
<th>Sleep-Activity</th>
<th>General Fatigue</th>
<th>General Symptoms</th>
<th>General Impairment</th>
<th>General Health</th>
<th>General Psychological</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major</td>
<td>FAI Global</td>
<td>SF-36 Physical</td>
<td>SF-36 Role</td>
<td>SF-36 General</td>
<td>Beck Depression</td>
</tr>
<tr>
<td></td>
<td>Fatigue Severity</td>
<td>Functioning Scale</td>
<td>Impairment:</td>
<td>Health</td>
<td>Inventory</td>
</tr>
<tr>
<td></td>
<td>Scale</td>
<td>Physical</td>
<td>Perceptions Scale</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amplitude</td>
<td>FAI Situation-</td>
<td>SF-36 Bodily Pain</td>
<td>SF-36 Role</td>
<td>SF-36 Health</td>
<td>POMS Depression</td>
</tr>
<tr>
<td></td>
<td>Specific Fatigue</td>
<td>Scale</td>
<td>Impairment:</td>
<td>Change Scale</td>
<td>Sub-scale</td>
</tr>
<tr>
<td></td>
<td>Scale</td>
<td>Emotional</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phase</td>
<td>FAI Fatigue:</td>
<td>POMS Confusion</td>
<td>SF-36 Social</td>
<td></td>
<td>POMS Anxiety</td>
</tr>
<tr>
<td></td>
<td>Consequences</td>
<td>Sub-scale</td>
<td>Functioning</td>
<td></td>
<td>Sub-scale</td>
</tr>
<tr>
<td></td>
<td>Scale</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>£</td>
<td>FAI Fatigue:</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Responsiveness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Scale</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>POMS Fatigue</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Sub-scale</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
appropriate adjustments made where necessary according to procedures outlined by Tabachnik and Fidell (1996).

An apparent difference in baseline BDI scores was noted, with the Light-Only group scoring somewhat lower than the three other treatment groups. One-way ANOVA found a significant effect F(3,36)=3.10, p<.05, although post hoc tests did not separate groups at the .05 level. Baseline BDI scores were, therefore, tested as covariates in all of the doubly-multivariate repeated measures ANOVAs and included when they made a significant contribution to results. A summary of the results of the six doubly multivariate analyses and post hoc tests is presented below, in Table 8.2, and elaborated in the following sections.

Table 8.2 shows that the overall result of the various analyses were the detection of two group by time interactions and a number of significant main effects for time. The group by time interactions were both related to fatigue, with the three therapeutic groups experiencing a reduction in fatigue severity between pre- and post-testing, compared to no change for the placebo group. The two CBT groups also experienced a significant increase in the responsiveness of fatigue to sleep, while the light only and placebo groups showed no significant change. Significant sample-wide improvements in a number of variables over time are also evident. The results of these analyses are elaborated upon in the following sections.
Table 8.2.
Results of doubly-multivariate repeated measures ANOVAs carried out for pre- and post data for each DV set.

<table>
<thead>
<tr>
<th>DV Set</th>
<th>Multivariate</th>
<th>Multivariate</th>
<th>Multivariate</th>
<th>Univariate</th>
<th>Nature of</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Group Main</td>
<td>Time Main</td>
<td>Group by</td>
<td>Interactions</td>
<td>Time Main</td>
</tr>
<tr>
<td></td>
<td>Effect</td>
<td>Effect</td>
<td>Time</td>
<td>Effect (Pre-</td>
<td>Post change)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Interaction</td>
<td>Post change</td>
<td></td>
</tr>
<tr>
<td>Sleep</td>
<td>F(12,105)=1.23</td>
<td>F(4,33)=3.27</td>
<td>F(12,105)=1.05</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>F(15,99)=0.62</td>
<td>F(5,31)=3.67</td>
<td>F(15,99)=1.98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td></td>
<td></td>
<td></td>
<td>F(3,35)=2.08</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gp 1 Sev ↓ at Post-treat</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gp 2 Sev ↓ at Post-treat</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gp 3 Sev ↓ at Post-treat</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gp 4 No sig change</td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>F(9,108)=1.32</td>
<td>F(3,34)=4.08</td>
<td>F(9,108)=0.66</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
<td>F(3,35)=3.88</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gp 1 Resp ↑ at Post-treat</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gp 2 Resp ↑ at Post-treat</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gp 3 Non-sig Trend ↑</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Gp 4 No sig change</td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>F(9,108)=0.90</td>
<td>F(3,34)=6.83</td>
<td>F(9,108)=1.36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impairment</td>
<td></td>
<td></td>
<td></td>
<td>↑ Role Physic ***</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ Social Funct **</td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>F(6,72)=0.25</td>
<td>F(2,24)=6.61</td>
<td>F(6,70)=1.22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Health</td>
<td></td>
<td></td>
<td></td>
<td>↑ Gen Health **</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ Hual change*</td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>F(9,108)=1.81</td>
<td>F(3,34)=0.75</td>
<td>F(9,108)=0.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Psychological</td>
<td></td>
<td></td>
<td></td>
<td>↑ Activity Ms</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ Activity Amp*</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>↑ Activity r*</td>
<td></td>
</tr>
</tbody>
</table>

* \( p<0.05 \)  ** \( p<0.01 \)  *** \( p<0.001 \)
Sleep-Activity Parameters

Interventions were designed with the specific aim of increasing sleep-activity amplitude via encouragement of appropriate daytime activity levels coupled with the consolidation and regularising of the nocturnal sleep period. The first doubly-multivariate repeated measures ANOVA was carried out in order to determine whether changes in rhythm parameters had occurred by post-intervention, and whether any of these changes were treatment specific.

Table 8.3 provides the group means and standard deviations for each of the four sleep-activity parameters. The lack of significant multivariate main effect for group, $F(12,105)=1.23$, $p>.05$, indicated that the groups did not differ overall on the dependent measures. Examination of trends indicates that the three therapeutic groups showed increases in activity levels, amplitude of the sleep activity rhythm as well as its goodness of fit to a 24-hour cycle. Sleep-Activity acrophase also tended to phase advance, as would be expected, given that this was a specific goal of treatment for a significant proportion of patients. However, these trends were not sufficiently different between groups, nor from the response of the
Table 8.3.

Group means and standard deviations for pre- and post-intervention sleep activity rhythm parameters

<table>
<thead>
<tr>
<th></th>
<th>Sleep-Activity</th>
<th>Sleep-Activity</th>
<th>Sleep-Activity</th>
<th>Sleep-Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mesor</td>
<td>Amplitude</td>
<td>Acrophase</td>
<td>r²</td>
</tr>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td>CBT + Light</td>
<td>M</td>
<td>.22</td>
<td>.08</td>
<td>2.41</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>.32</td>
<td>.34</td>
<td>.22</td>
</tr>
<tr>
<td>CBT + Placebo</td>
<td>M</td>
<td>.31</td>
<td>.16</td>
<td>2.31</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>.32</td>
<td>.28</td>
<td>.36</td>
</tr>
<tr>
<td>Light</td>
<td>M</td>
<td>.16</td>
<td>.14</td>
<td>2.41</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>.33</td>
<td>.20</td>
<td>.27</td>
</tr>
<tr>
<td>Placebo</td>
<td>M</td>
<td>.37</td>
<td>.22</td>
<td>2.17</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>.34</td>
<td>.22</td>
<td>.31</td>
</tr>
<tr>
<td>Total</td>
<td>M</td>
<td>-.27</td>
<td>-.15</td>
<td>2.32</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>.32</td>
<td>.26</td>
<td>.30</td>
</tr>
</tbody>
</table>

* p < .05  ** p < .01  *** p < .001

placebo group, to achieve a multivariate group by time interaction F(12,105)=1.05, p>.05. A significant multivariate main effect for Time was present F(4,33)=3.27, p<.05, which indicated that, after collapsing across groups, the combination of DVs changed significantly from pre- to post-intervention. Follow-up univariate tests indicated significant overall (i.e. across all participants) improvements in sleep-activity mesor F(1,36)=9.66, p<.005, amplitude F(1,36)=7.02, p<.05, and goodness of fit F(1,36)=4.88,
p<.05. The overall phase advance, however, did not achieve significance $F(1,36)=2.32$, p>.05.

Thus, with respect to the sleep-activity rhythm, while the intervention groups did not differ from the placebo group nor from each other in their responses to treatment, general increases in activity levels, amplitude of the sleep-activity rhythm, and in its adequacy of fit to a 24-hour cycle were found across the sample.

*General Fatigue Measures*

Examination of Table 8.4 reveals trends towards improvement across the outcome measures associated with fatigue. In general, these were small in magnitude and present across all groups, including the placebo-control group. The two exceptions are the fatigue severity and fatigue responsiveness measures, in which improvements appear to have occurred in the three therapeutic conditions but not in the placebo group.

As BDI scores were found to act as a significant covariate $F(3,31)=2.62$, p<.05, they were included in the doubly-multivariate repeated measures ANOVA and follow-up analyses, where they also made a significant contribution. A significant multivariate group by time interaction $F(15,99)=1.98$, p<.05 was found via the doubly-multivariate repeated measures MANOVA, indicating that significant changes occurred over time on
the combination of general fatigue measures, and that the nature of these changes was different across treatment groups. Follow-up two-way univariate repeated measures ANOVAs on each of the DVs found significant group by time interactions for scores on the FAI Global Fatigue Severity Scale $F(3,35)=2.88$, $p<.05$ as well as for scores on the FAI Fatigue Responsiveness Scale $F(3,35)=3.88$, $p<.05$. Examination of time effects for each group found significant reductions in Fatigue Severity Scores in the CBT+Light group $F(1,9)=8.65$, $p<.05$, the CBT+Placebo group $F(1,9)=11.38$, $p<.01$, and the Light only group $F(1,9)=8.74$, $p<.05$. In contrast, the Placebo only group experienced no change overall on this measure $F(1,9)=0.01$, $p>.05$. For fatigue responsiveness to sleep and/or rest, significant improvements were experienced in the CBT+Light group $F(1,9)=8.147$, $p<.05$ and the CBT+Placebo group $F(1,9)=5.13$, $p<.05$. The apparent improvement in the Light Only group just failed to attain significance $F(1,9)=4.46$, $p>.05$ ($p=.06$), and no change was experienced by the Placebo Only group $F(1,9)=0.02$, $p>.05$.

An overall main effect for time was also present $F(5,31)=3.67$, $p<.05$, with sample-wide decreases in FAI Fatigue Consequences Scale scores $F(1,35)=6.99$, $p<.05$ and the POMS Fatigue Sub-scale $F(1,35)=22.97$, $p<.001$. No change was found for the FAI Situation-Specific Fatigue Scale $F(1,36)=0.49$, $p>.05$. No overall main effect for group was detected $F(15,99)=0.62$, $p>.05$. 
Table 8.4.

Group means and standard deviations for pre-and post-intervention general fatigue measures.

<table>
<thead>
<tr>
<th>Score range</th>
<th>Severity</th>
<th>Specificity</th>
<th>Consequences</th>
<th>Responsiveness</th>
<th>Sub-scale</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.77-22.50</td>
<td>6-42</td>
<td>3-21</td>
<td>2-14</td>
<td>0-21</td>
<td></td>
</tr>
</tbody>
</table>

High scores indicate:
- Increased fatigue
- Fatigue results from specific stimuli
- Greater impact on general functioning
- More responsive to sleep/rest
- Increased fatigue

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
<th>Pre</th>
<th>Post</th>
<th>Pre</th>
<th>Post</th>
<th>Pre</th>
<th>Post</th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBT + Light</td>
<td>M</td>
<td>73.10</td>
<td>68.90*</td>
<td>21.10</td>
<td>20.80</td>
<td>16.80</td>
<td>15.90</td>
<td>7.20</td>
<td>10.10*</td>
<td>19.20</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>4.04</td>
<td>6.40</td>
<td>4.38</td>
<td>7.45</td>
<td>3.19</td>
<td>3.48</td>
<td>3.68</td>
<td>3.48</td>
<td>3.77</td>
</tr>
<tr>
<td>CBT + Placebo</td>
<td>M</td>
<td>72.60</td>
<td>67.30*</td>
<td>22.80</td>
<td>25.00</td>
<td>16.40</td>
<td>15.70</td>
<td>9.40</td>
<td>10.60*</td>
<td>20.30</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>4.53</td>
<td>9.03</td>
<td>5.16</td>
<td>5.83</td>
<td>1.784</td>
<td>2.67</td>
<td>3.89</td>
<td>3.49</td>
<td>4.60</td>
</tr>
<tr>
<td>Light</td>
<td>M</td>
<td>67.80</td>
<td>63.60*</td>
<td>23.10</td>
<td>23.70</td>
<td>15.10</td>
<td>15.20</td>
<td>9.40</td>
<td>10.70</td>
<td>16.70</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>6.76</td>
<td>7.59</td>
<td>5.49</td>
<td>6.91</td>
<td>2.96</td>
<td>2.97</td>
<td>3.37</td>
<td>2.06</td>
<td>4.90</td>
</tr>
<tr>
<td>Placebo</td>
<td>M</td>
<td>70.80</td>
<td>70.90</td>
<td>24.20</td>
<td>24.50</td>
<td>16.80</td>
<td>15.40</td>
<td>9.50</td>
<td>9.60</td>
<td>20.80</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>4.29</td>
<td>4.80</td>
<td>7.45</td>
<td>4.88</td>
<td>3.26</td>
<td>4.27</td>
<td>2.55</td>
<td>3.37</td>
<td>3.91</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
<th>Pre</th>
<th>Post</th>
<th>Pre</th>
<th>Post</th>
<th>Pre</th>
<th>Post</th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>M</td>
<td>71.08</td>
<td>67.68</td>
<td>22.80</td>
<td>23.30</td>
<td>16.28</td>
<td>15.55*</td>
<td>8.88</td>
<td>10.30</td>
<td>19.25</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>5.26</td>
<td>7.37</td>
<td>5.62</td>
<td>6.32</td>
<td>2.84</td>
<td>3.28</td>
<td>3.42</td>
<td>3.07</td>
<td>4.92</td>
</tr>
</tbody>
</table>

*p < .05  **p < .01  ***p < .001

Thus, small but significant decreases in fatigue severity were experienced by the three therapeutic groups over the intervention period, while the placebo group experienced no change. Therapeutic groups, in contrast with the Placebo Only group, also experienced
small but significant improvements in the responsiveness of their fatigue to sleep and/or rest. Decreases in the negative consequences of fatigue and scores on the POMS Fatigue Subscale occurred across the entire sample.

*General Symptom Measures*

The data in Table 8.5 indicate general but small improvements on all measures of general symptoms across all four groups, the only exception being a slightly poorer score at post intervention for the bodily pain scale for the Placebo group. No significant multivariate group by time interaction was found for the general symptom DVs $F(9,108)=0.66$, $p>.05$, nor was there any main effect for group $F(9,108)=1.32$, $p>.05$. A significant main effect for time was found $F(3,34)=4.08$, $p<.05$, indicating that, overall, there were sample-wide changes on the combination of DVs. The time main effect was followed up by univariate repeated measures ANOVAs for each of the DVs, which found a significant reduction in POMS Confusion scores at post-intervention $F(1,36)=8.96$, $p<.01$. No time effect was present on the SF-36 Physical Functioning Scale $F(1,36)=2.29$, $p>.05$, nor on the SF-36 Bodily Pain Scale $F(1,36)=3.18$, $p>.05$. 
Table 8.5.

Group means and standard deviations for pre-and post-intervention general symptom measures.

<table>
<thead>
<tr>
<th></th>
<th>SF-36 Physical Functioning</th>
<th>SF-36 Bodily Pain</th>
<th>POMS Confusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score range</td>
<td>0-100</td>
<td>0-100</td>
<td>0-21</td>
</tr>
<tr>
<td>High scores</td>
<td>Fewer limitations</td>
<td>Less pain</td>
<td>More confusion</td>
</tr>
<tr>
<td>indicate:</td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
</tr>
<tr>
<td>CBT M</td>
<td>31.00</td>
<td>38.00</td>
<td>48.70</td>
</tr>
<tr>
<td>+ SD</td>
<td>21.45</td>
<td>26.16</td>
<td>20.66</td>
</tr>
<tr>
<td>Light</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBT M</td>
<td>33.00</td>
<td>34.00</td>
<td>58.80</td>
</tr>
<tr>
<td>+ SD</td>
<td>19.75</td>
<td>22.09</td>
<td>18.99</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>46.50</td>
<td>51.50</td>
<td>49.50</td>
</tr>
<tr>
<td>Light SD</td>
<td>18.57</td>
<td>26.15</td>
<td>13.99</td>
</tr>
<tr>
<td>M</td>
<td>27.00</td>
<td>29.50</td>
<td>46.40</td>
</tr>
<tr>
<td>Placebo SD</td>
<td>15.85</td>
<td>14.99</td>
<td>13.55</td>
</tr>
<tr>
<td>Total</td>
<td>34.38</td>
<td>38.25</td>
<td>50.85</td>
</tr>
<tr>
<td>SD</td>
<td>19.72</td>
<td>23.44</td>
<td>17.09</td>
</tr>
</tbody>
</table>

*p < .05  **p < .01  ***p < .001

Thus, other than a sample-wide improvement on the POMS Confusion Subscale, no significant effects were found for the General Symptom measures over the intervention period.
General Impairment Measures

The data in Table 8.6 indicate general improvements across all groups for the SF-36 Role Functioning (Physical) Scale and SF-36 Social functioning Scale scores. All groups, apart from the CBT+Light group appeared to make small gains on the SF-36 Role Functioning (Emotional) Scale. Results of the doubly-multivariate repeated measures ANOVA with the general impairment DVs indicated no overall group by time interaction \( F(9,108)=1.36, p>.05 \), and no overall main effect for group \( F(9,108)=0.90, p>.05 \). A significant multivariate main effect for time was present \( F(3,34)=6.83, p<.01 \), indicating a general improvement over time on the combination of DVs across all groups. Univariate repeated measures ANOVAs for each of the DVs demonstrated that significant improvements occurred on the SF-36 Role Functioning (Physical) \( F(1,36)=16.01, p<.001 \) and SF-36 Social Functioning Scale \( F(1,36)=14.56, p<.005 \). No significant change was found for the SF-36 Role Functioning (Emotional) Scale \( F(1,36)=2.58, p>.05 \). Thus, sample-wide improvements occurred over the treatment period on measures of social functioning and role impairment due to physical factors, but no group effects were apparent on the General Impairment measures.
Table 8.6.

Group means and standard deviations for pre-and post-intervention general impairment scores.

<table>
<thead>
<tr>
<th></th>
<th>SF-36 Role</th>
<th>SF-36 Role</th>
<th>SF-36</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Functioning</td>
<td>Functioning</td>
<td>Social Functioning</td>
</tr>
<tr>
<td></td>
<td>Physical</td>
<td>Emotional</td>
<td></td>
</tr>
<tr>
<td>Score range</td>
<td>0-100</td>
<td>0-100</td>
<td>0-100</td>
</tr>
<tr>
<td>High scores</td>
<td>Fewer limitations</td>
<td>Fewer limitations</td>
<td>Fewer limitations</td>
</tr>
<tr>
<td>indicate</td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
</tr>
<tr>
<td>CBT</td>
<td>M</td>
<td>0.00</td>
<td>3.75</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.00</td>
<td>8.45</td>
</tr>
<tr>
<td>Light</td>
<td>CBT</td>
<td>M</td>
<td>0.00</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD</td>
<td>0.00</td>
</tr>
<tr>
<td>Placebo</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>6.25</td>
<td>10.00</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>13.50</td>
<td>17.48</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>M</td>
<td>0.00</td>
<td>3.75</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>0.00</td>
<td>8.44</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Total</td>
<td>M</td>
<td>1.56</td>
</tr>
<tr>
<td></td>
<td></td>
<td>SD</td>
<td>7.04</td>
</tr>
</tbody>
</table>

p < .05  ** p < .01  *** p < .001
**General Health Measures**

Table 8.7.

Group means and standard deviations for pre-and post-intervention general health scores.

<table>
<thead>
<tr>
<th></th>
<th>SF-36 General Health</th>
<th>SF-36 Health Transition</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Score range:</strong></td>
<td>0-100</td>
<td>0-100</td>
</tr>
<tr>
<td><strong>High scores</strong></td>
<td>More positive perceptions of health status</td>
<td>Perceives health as improved compared to a year ago</td>
</tr>
<tr>
<td><strong>indicate:</strong></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td><strong>CBT</strong></td>
<td>M</td>
<td>27.40</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>18.12</td>
</tr>
<tr>
<td><strong>Light</strong></td>
<td>M</td>
<td>21.50</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>10.01</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>M</td>
<td>32.90</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>16.12</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>M</td>
<td>27.00</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>17.35</td>
</tr>
</tbody>
</table>

* M: Mean, SD: Standard Deviation

* p <.05 ** p <.01 *** p <.001
BDI scores were found to act as a significant covariate for the General Health measures $F(2,34)=3.50, p<.05$, and were therefore included in the analyses. Table 8.7 reveals that, although general small improvements on the SF-36 General Health Perceptions and SF-36 Health Change scales appear to have occurred in the three therapeutic groups with negative or no change in the placebo group, the doubly-multivariate repeated measures ANOVA found no significant overall group by time interaction $F(6,70)=1.22, p>.05$. No overall group main effect was present $F(6,70)=0.25, p>.05$, however, there was a significant multivariate change in the DVs over time $F(2,34)=6.61, p<.05$. Examination of the individual time main effect for each DV found significant improvements on the SF-36 General Health Perceptions Scale $F(1,35)=7.76, p<.01$, and on the SF-36 Health Transition Scale $F(1,35)=7.14, p<.05$ occurred at post-intervention across the groups. Thus, while significant improvements in general health status and general health perceptions occurred over the entire sample, group differences were not present.

**General Psychological Measures**

As reported earlier, baseline BDI scores for the Light Only group appeared to be lower than those of the other groups and, while a significant overall effect was found, post-hoc between-group contrasts failed to separate any of the groups at the .05 level. Examination of Table 8.8 reveals no clear trends on the depression and anxiety scales, apart from a general small reduction in BDI scores over time. Doubly-multivariate repeated measures ANOVA found no overall significant group by time interaction.
\( F(9,108) = 0.45, \ p > .05 \) nor an overall main effect for group \( F(9,108) = 1.81, \ p > .05 \) or time \( F(3,34) = 0.75, \ p > .05 \) on the general psychological variables.

### Table 8.8.

**Group means and standard deviations for pre-and post-intervention general psychological functioning.**

<table>
<thead>
<tr>
<th>Score range</th>
<th>Beck Depression</th>
<th>POMS Depression</th>
<th>POMS Anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-63</td>
<td>0-45</td>
<td>0-18</td>
<td></td>
</tr>
<tr>
<td>High scores indicate:</td>
<td>More depressive symptoms</td>
<td>More depressive symptoms</td>
<td>More anxiety symptoms</td>
</tr>
<tr>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td><strong>CBT</strong></td>
<td>M</td>
<td>11.80</td>
<td>10.70</td>
</tr>
<tr>
<td>+</td>
<td>SD</td>
<td>4.89</td>
<td>4.85</td>
</tr>
<tr>
<td><strong>Light</strong></td>
<td>M</td>
<td>14.90</td>
<td>14.20</td>
</tr>
<tr>
<td>+</td>
<td>SD</td>
<td>7.09</td>
<td>7.58</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>M</td>
<td>8.10</td>
<td>6.90</td>
</tr>
<tr>
<td><strong>Light</strong></td>
<td>SD</td>
<td>4.33</td>
<td>2.77</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>M</td>
<td>14.80</td>
<td>13.10</td>
</tr>
<tr>
<td>+</td>
<td>SD</td>
<td>6.29</td>
<td>6.31</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>M</td>
<td>12.40</td>
<td>11.23</td>
</tr>
<tr>
<td>+</td>
<td>SD</td>
<td>6.21</td>
<td>6.14</td>
</tr>
</tbody>
</table>

\( p < .05, \ *p < .01, \ **p < .001 \)
Relationships Between Sleep-Activity Parameters and Outcome Measures.

In order to examine whether the sample-wide significant improvements in outcome measures were associated with the changes in sleep-activity parameters, change scores were calculated by subtracting each participant’s score pre-intervention from the corresponding post-intervention value. This was done for all four sleep-activity parameters and for the two fatigue measures that demonstrated group by time interaction effects. These change scores were then correlated using Pearson’s r and results are presented in Table 8.9.

Table 8.9.

Pearson’s correlation coefficients for the relationships between pre-post changes in sleep-activity parameters and outcome measures for which significant treatment effects were detected.

<table>
<thead>
<tr>
<th>Outcome variable</th>
<th>Sleep-activity</th>
<th>Sleep-activity</th>
<th>Sleep-activity</th>
<th>Sleep-activity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mesor</td>
<td>Phase</td>
<td>Amplitude</td>
<td>r²</td>
</tr>
<tr>
<td>FAI Global Fatigue</td>
<td>.06</td>
<td>-.25</td>
<td>-.31 *</td>
<td>-.45 **</td>
</tr>
<tr>
<td>Severity Scale</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAI Fatigue</td>
<td>.10</td>
<td>.20</td>
<td>.26</td>
<td>.39 *</td>
</tr>
<tr>
<td>Responsiveness Scale</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* p<.05 ** p<.01 *** p<.001

Table 8.9 demonstrates that the significant increases in sleep-activity rhythm amplitude and goodness of fit to a 24-hour cycle were associated with the significant reductions in global fatigue severity scores (r=-.31, p<.05 and r=-.45, p<.01 respectively). Improvements in the goodness of fit of the sleep-activity rhythm to a 24-hour period
were also associated with improved responsiveness of fatigue to sleep and/or rest \( r = .39, p < .05 \). Reductions in global fatigue severity ratings were also weakly but significantly correlated with increases in the responsiveness of fatigue to sleep and/or rest \( r = - .31, p < .05 \). Changes in sleep-activity mesor and phase were not associated with fatigue outcomes.

**Discussion**

The aim of this study was to investigate whether treatments that were designed to facilitate the functioning of the internal circadian timekeeping system would relieve the symptoms of chronic fatigue syndrome. The results indicate these prototypical treatments led to some small but statistically significant gains, over and above those attributable to a placebo response, with respect to global fatigue severity and its responsiveness to sleep and/or rest. However, although patients showed overall improvements in general health, physical and social impairment and confusion, these were not significantly greater, or more consistent, than what occurred in patients subjected to placebo treatment. The three therapeutic protocols, CBT+Light, CBT+Placebo Light and Light alone could not be separated in terms of efficacy on any of the measures except for those assessing the responsiveness of fatigue to sleep and/or rest. For this variable, only the two CBT treatments led to a significant improvement.
Even so, a strong non-significant trend in the same direction occurred in the Light-Only group.

Although a major aim of treatments was to increase the salience of the sleep-activity rhythm via the regularisation and consolidation of the nocturnal sleep and daytime activity phases, sleep-activity parameters did not improve to a significantly greater degree in the therapeutic groups compared to the placebo group. Nevertheless, significant sample-wide improvements were found for sleep-activity mesor, amplitude and the goodness of fit to a 24-hour cycle. While the sleep-activity rhythms of the therapeutic groups advanced by more than a half hour on average, the result was not consistent enough to achieve significance. It is interesting, however, that improvements with respect to sleep-activity amplitude and goodness of fit were associated with improvements in fatigue severity, while the significant improvement in goodness of fit was also related to improvements in the responsiveness of fatigue to sleep and/or rest. Further, decreases in fatigue severity were related to the increases in its responsiveness to sleep. A possible explanation for these interrelationships would be that improvements in circadian functioning associated with the changes in sleep-activity parameters led to improved sleep quality, perhaps in terms of sleep structure and/or consolidation, which, in turn, reduced the severity of fatigue experienced by the patients. The fact that improvements in the responsiveness of fatigue to sleep were only significant in the two CBT groups, where sleep quality was a focus of intervention, supports this idea. Thus, although the clinical significance of the small gains made in these areas is questionable,
the fact that they were related to intervention targets is encouraging, and may indicate that more sustained, focused and/or intense interventions of similar type could produce improvements of greater magnitude.

Other behavioural intervention studies have achieved substantially greater treatment gains than those that were observed in the current study. Sharpe et al. (1996) studied the effectiveness of a 16 session CBT treatment protocol (plus normal medical care) in CFS sufferers compared to a control group who were offered normal medical care only. At 12 month follow-up, 73% of their CBT group had achieved satisfactory outcomes compared to only 27% of the control group. A similar trial of CBT in CFS patients, carried out by Deale et al. (1998), achieved a similar result. In this case, 70% of completers of a 13 session CBT program reported substantial clinical improvement, compared to only 19% of patients allocated to a relaxation training program. A 12-week graded exercise program led to an average increase in SF-36 physical functioning scores of 20.5 points in CFS patients monitored by Fulcher and White (1997), which compares with the 5 point increase experienced by the CFS group in the current study.

Comparisons must, however consider that the intervention applied in the current study was of substantially shorter duration than those applied in these trials. In the studies by Sharpe et al. (1996) and Deale et al. (1998), the main treatment effectiveness measures reported were not immediate post-treatment, but at 12 and 6 months follow-up respectively. Participants in the current study were also longer-term sufferers in general (6.47 years) compared to the combined mean of 2.96 years of those participating in the
studies outlined above (Deale et al., 1998; Fulcher & White, 1997; Sharpe et al., 1996). Fulcher and White (1997) also did not include participants who qualified for comorbid psychiatric diagnoses, such as major depression or anxiety disorders, a factor that is likely to have further improved the likelihood of achieving a treatment effect.

An earlier study of CBT, carried out over a similar time-frame and with a patient group of similar illness duration (5.5 years) to the current study also failed to find significant treatment effects (Lloyd et al., 1993). These authors pointed out that their intervention may not have been of sufficient intensity or duration to have produced significant changes. While it may be that longer treatment programs are necessary for the treatment of people with CFS, this was not considered to be so for the purposes of the current study. This was because, even without assistance, the most jet-lagged individuals generally take no more than two weeks to recover (Binkley, 1990; Boulos et al., 1995). The use of bright light, melatonin and/or behavioural interventions substantially speeds the reentrainment process, in most cases reducing it to a few days (Armstrong, 1991; Boulos et al., 1995). Six-weeks of bright light and/or behavioural intervention was seen, therefore, as sufficient, even considering the possibility that the circadian systems of people with CFS may not be as responsive as those of healthy individuals. Anecdotally, this appeared to be a valid assumption, given that during treatment, patients appeared to respond to the light exposure in much the same way as other individuals do and, where attempted, phase advances of the sleep-wake cycle were no more difficult to achieve.
Nevertheless, whether it was because of inadequacy of the treatment protocol, or some kind of pathological intransigence of the circadian systems of CFS patients, the possibility that intervention was not successful in restoring circadian integrity to a significant extent in the majority of patients cannot be discounted. Due to practical constraints, no specific pre-post measures of behavioural-physiologic circadian integrity were collected, and it is not, therefore, possible to assess whether the lack of substantial clinical effect was due to a lack of treatment impact on circadian functioning. The absence of significant treatment by time interaction effects with respect to the sleep-activity cycle measures may be indicative of this, although factors such as small sample size and limited sensitivity of the self-report instrument are probably more significant in this respect.

Given the trends demonstrated in the outcome data, and anecdotal reports of patients, it appears more likely that the interventions were successful to some degree in restoring circadian integrity. Two further possibilities could account for the lack of treatment impact with respect to the symptomatology of the disorder. The first is that, while treatment intensity and duration may have been sufficient for the systems of CFS patients to reentrain, it may not have been long enough for reentrainment to have had a substantial impact upon a chronically entrenched symptom complex. A longer treatment period may, therefore, have provided more time for the beneficial effects of the
integration of the circadian system to impact upon symptomatology. The second possibility, and perhaps most obvious, is that circadian desynchrony is merely an epiphenomenon of the disorder and, therefore, has no real significance with respect to its aetiology or persistence. While this may well be the case, it would be premature to accept such a position until studies in which the effects of treatments are assessed where the restoration of internal and external circadian synchrony is clearly established by appropriate pre- and post-assessment of physiological and behavioural circadian functioning.

Further work is clearly required to provide answers to the questions raised or left open by the current protocol. Longer-term interventions would provide more time for any potentially beneficial effects to manifest. Given that the requirements of daily light exposure sessions can be quite restricting, other less arduous intervention strategies might lend themselves better to longer-term studies, reducing the likelihood of confounds due to treatment non-compliance. Possibilities include the use of natural light which, even on cloudy days, is brighter than that usually available from commercial light-boxes (Morita & Tokura, 1998), or perhaps the trialing of regular administration of melatonin to CFS patients. Melatonin trials might still, however, require intermittent light exposure sessions as, although melatonin administration is capable of producing phase shifts of sleep and core temperature rhythms in either direction, it has only limited effectiveness with respect to the consistent synchronization of physiological rhythms (Arendt & Deacon, 1997; Middleton, Arendt & Stone, 1997). Another potentially
valuable avenue for future work would be the use of single case interventions, in which intervention and monitoring could be more intense as well as more easily manipulated. Results of such studies could be used to refine treatments that could then be tested on a larger scale.

With regard to the current protocol, however, the question remains as to whether the lack of improvement over and above that associated with a placebo response was due, in part at least, to the lack of time allowed for potential treatment effects to manifest. This may be particularly relevant to the groups who received CBT, given that significant treatment responses demonstrated by previous research took at least 6 months to appear (Deale et al., 1998; Sharpe et al., 1996). The following, and final, experimental chapter describes the results of a longer term follow-up designed to examine this issue.
CHAPTER 9

STUDY 5: SIX-MONTH FOLLOW-UP OF PATIENTS INVOLVED IN THE CLINICAL INTERVENTION STUDY
Introduction

The previous chapter described the results of a placebo controlled treatment trial of clinical interventions designed to restore circadian integrity to patients diagnosed with CFS. These interventions entailed the use of bright light exposure and cognitive-behaviour therapy (CBT), alone and in combination with each other, in an attempt to externally and internally resynchronise the circadian systems of CFS patients. As outlined in Study 4, the only measures on which the therapeutic interventions performed significantly better than the placebo response was in producing a small but significant decrease in fatigue severity and, for the CBT interventions, an increase in fatigue responsiveness to sleep and/or rest. While general improvements occurred across the sample on a number of other health outcome measures, these were also small in magnitude and no different to those achieved by the placebo group.

These results compare poorly with those of other recent investigations of behavioural interventions, including CBT (Deale et al., 1998; Sharpe et al., 1996) and graded exercise programs (Fulcher & White, 1997; Wearden et al., 1998) for CFS patients, in which substantial treatment effects were reported. In discussing the possible reasons for the relative lack of response to the current treatment, one area that was noted was that the relatively short follow-up time of 8 weeks may not have been long enough for any potentially beneficial effects to manifest themselves. In those studies outlined above,
the minimum follow-up was 12 weeks for the graded exercise studies (Fulcher & White, 1997; Wearden et al., 1998) and 6-12 months for the CBT studies (Deale et al., 1998; Sharpe et al., 1996). At 12 weeks, Fulcher and White (1997) found significant improvements in their highly selected sample of non-depressed or anxious CFS patients. Only modest and mostly non-significant gains were apparent after the same time period in the Wearden et al. (1998) study, which tested a sample more representative of the CFS population in general. In the two recent CBT studies, significant improvements were not noted until at least six months following treatment (Deale et al., 1998; Sharpe et al., 1996), with both groups reporting continued improvements in their patients occurring after intervention had finished.

It would be reasonable to hypothesise that several aspects of the treatments trialed in Study 4 could also lead to continued improvements after the conclusion of the formal treatment process. The CBT treatments, in particular, with elements such as education about healthy sleep behaviour and cognitive restructuring with a focus on reducing avoidance of physical, mental and social activities, may take some time to have an appreciable impact. Even in the light-only treatment, raising awareness about the importance of regular sleep-wake patterns and exposure to a salient light-dark cycle could affect the behaviour of participants in the longer term, with improvements in symptomatology occurring as a result.
With this in mind, a 6-month follow-up of participants in the original treatment study was initiated. The main aims of this study were to assess whether: a) treatment gains with respect to fatigue severity and responsiveness to sleep and/or rest were maintained over time; b) improvements on these or other outcome variables occurred following the conclusion of treatment and; c) treatment groups differed in their responses over time.

**Method**

**Participants**

Participants from the three therapeutic groups in Study 4 were followed up. Participants from the placebo group could not be included as a significant proportion had taken up the offer of CBT+Light or Light only treatment following the original trial. In total, 28 out of a possible 30 participants responded to the 6-month follow up survey (5 males and 23 females). These participants ranged in age from 19 to 68 years ($M=39.43$; $SD=12.15$), and in illness duration from 2 to 32 years ($M=7.14$; $SD=6.01$).

**Materials and Procedure**

Participants were informed about the likelihood that they would be followed up at around 6-months at the time of the original study, and had thereby agreed to be
recontacted. Each participant was contacted for this purpose at approximately 6 months from when they had first commenced treatment, which meant that follow-up was generally 4 months after treatment had concluded. One male participant had changed residence without leaving a forwarding address and was unable to be contacted. All other participants were contacted and agreed to participate in the follow-up procedure, and were delivered the appropriate materials either by mail or by hand. The same outcome measures were administered as in the previous study (BDI, POMS, MOS SF-36 and the two-week sleep-activity diary). A postage paid return addressed envelope was provided with the materials, and participants were asked to complete the questionnaires and diary within 3 weeks and send them back to the investigator. Participants who had not responded in this time period were recontacted. Only one participant of the 29 contacted did not return the follow-up surveys, at first indicating that they had not received the original materials and then failed to respond to subsequent contact attempts. Overall, 28 of the 30 original participants from the therapeutic groups responded at follow-up. The two non-respondents were both originally from the CBT+Placebo Light group.

**Results**

Data were screened, cleaned and analysed in the same manner as in Study 4. Table 9.1 presents a summary of results of the doubly-multivariate repeated measures ANOVAs carried out for each DV set across the three intervention groups. The two independent
variables were group (CBT+Light, CBT+Placebo and Light only) and time (pre-intervention, post-intervention and six month follow-up) and DV sets were the same as for the analysis of the pre-post intervention data reported in the previous chapter. The aim of the analysis was to assess whether the three intervention groups responded to treatment differently over time, and also to investigate whether general improvements noted at post-intervention were maintained six-months after the beginning of treatment.

Examination of Table 9.1 reveals that no significant group by time interactions were found for any of the doubly-multivariate repeated measures ANOVAs. This indicates that the three treatment groups did not differ in the way the sets of DVs changed over time. A single significant group main effect was found for the DV set pertaining to psychological functioning, and further analysis revealed that the Light only group scored significantly lower on the BDI overall, across the three time points. This group had lower BDI scores at baseline, and this trend was carried through post-treatment and follow-up. As was discussed previously, this finding is likely to be due to sampling error and not related to any effect of treatment. Nonetheless, differential levels of depression was a potential confounding factor and, as in the pre- to post-intervention study, baseline BDI scores were tested as covariates in the analyses and included where significant. BDI scores were found to significantly impact upon measures of General Fatigue and General Health.
As demonstrated in Table 9.1, significant main effects for time were present for General Impairment and for General Psychological Functioning. Follow-up univariate analyses for the effects found no changes in any of the variables, apart from an improvement in BDI score, which occurred between post-intervention and follow-up, and the maintenance of the small but significant improvements in general impairment measures that had occurred between pre-and post-intervention.

Table 9.1.
Results of Doubly-multivariate repeated measures ANOVAs carried out for pre-intervention, post-intervention and follow-up data for each DV set for the three intervention groups.

<table>
<thead>
<tr>
<th>DV Set</th>
<th>Multivariate Group Main Effect</th>
<th>Multivariate Time Main Effect</th>
<th>Multivariate Group by Time Interaction</th>
<th>Nature of Time Main Effect</th>
<th>Point of Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep-Activity</td>
<td>$F(8,46)=0.57$</td>
<td>$F(8,96)=1.82$</td>
<td>$F(16,200)=0.68$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Fatigue</td>
<td>$F(10,44)=1.75$</td>
<td>$F(10,90)=1.65$</td>
<td>$F(20,188)=1.04$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Symptoms</td>
<td>$F(6,48)=1.04$</td>
<td>$F(6,98)=0.68$</td>
<td>$F(12,150)=1.00$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Impairment</td>
<td>$F(6,48)=1.50$</td>
<td>$F(6,98)=2.32$</td>
<td>$F(12,150)=1.47$</td>
<td>$\uparrow$ Role (Phys) $^{**}$</td>
<td>$\uparrow^*$$ \uparrow^{**}$</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>$\uparrow$ Social Func.  $^{*}$</td>
<td>$\uparrow^*$$ \uparrow^{**}$</td>
</tr>
<tr>
<td>General Health</td>
<td>$F(4,50)=.73$</td>
<td>$F(4,96)=1.98$</td>
<td>$F(8,96)=0.74$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>General Psychological Health</td>
<td>$F(6,48)=3.23$</td>
<td>$F(6,98)=2.33$</td>
<td>$F(12,150)=0.38$</td>
<td>$\downarrow$ BDI $^{**}$</td>
<td>$\downarrow^*$</td>
</tr>
</tbody>
</table>

$p<.05$, $^{*}p<.01$, $^{**}p<.001$
**Sleep-activity parameters**

Table 9.2 reveals that, by 6-month follow-up, there had been a general, although, for the most part, incomplete, deterioration of the significant improvements found between pre- and post-intervention. Doubly-multivariate repeated measures ANOVA found no overall significant group by time interaction $F(16,200)=0.68$, $p>.05$, and no overall main effect for group $F(8,46)=0.57$, $p>.05$.

**Table 9.2.**

**Means and standard deviations for the four rhythm parameters for sleep-activity for each of the three intervention groups at pre- and post-intervention and follow-up.**

<table>
<thead>
<tr>
<th></th>
<th>Sleep-Activity Mesor</th>
<th>Sleep-Activity Amplitude</th>
<th>Sleep-Activity Acrophase</th>
<th>Sleep-Activity $r^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Follow</td>
<td>Pre</td>
</tr>
<tr>
<td><strong>CBT</strong></td>
<td>.22</td>
<td>.08</td>
<td>-.12</td>
<td>2.41</td>
</tr>
<tr>
<td>$+$</td>
<td>.32</td>
<td>.34</td>
<td>.37</td>
<td>.24</td>
</tr>
<tr>
<td><strong>Light</strong></td>
<td>.31</td>
<td>-.16</td>
<td>-.19</td>
<td>2.31</td>
</tr>
<tr>
<td>$+$</td>
<td>.32</td>
<td>.28</td>
<td>.43</td>
<td>.36</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>-.16</td>
<td>-.14</td>
<td>-.14</td>
<td>2.41</td>
</tr>
<tr>
<td>$+$</td>
<td>.32</td>
<td>.20</td>
<td>.28</td>
<td>.27</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>-.23</td>
<td>-.13</td>
<td>-.15</td>
<td>2.37</td>
</tr>
<tr>
<td>$+$</td>
<td>.32</td>
<td>.27</td>
<td>.35</td>
<td>.29</td>
</tr>
</tbody>
</table>

*p <.05, **p <.01, ***p <.001*
The main effect for time approached, but did not attain significance $F(8.96)=1.82$, $p>.05$ ($p=.08$). This indicates that gains in the areas of sleep-activity mesor, amplitude and goodness of fit to a 24-hour period were not maintained during the follow-up period.

**General Fatigue Measures**

**Table 9.3.**

*Means and standard deviations for the outcome measures of General Fatigue for each of the three intervention groups at pre- and post-intervention and follow-up.*

<table>
<thead>
<tr>
<th></th>
<th>FAI Severity</th>
<th>FAI Specificity</th>
<th>FAI Consequences</th>
<th>FAI Responsiveness</th>
<th>POMS Fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Follow</td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td><strong>CBT</strong></td>
<td>73.10</td>
<td>68.99</td>
<td>67.90</td>
<td>21.10</td>
<td>20.80</td>
</tr>
<tr>
<td></td>
<td>± 4.04</td>
<td>6.40</td>
<td>11.96</td>
<td>4.28</td>
<td>7.45</td>
</tr>
<tr>
<td><strong>Light</strong></td>
<td>72.60</td>
<td>67.30</td>
<td>59.50</td>
<td>22.80</td>
<td>25.00</td>
</tr>
<tr>
<td></td>
<td>± 4.53</td>
<td>9.03</td>
<td>14.03</td>
<td>5.16</td>
<td>5.83</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td>67.80</td>
<td>63.60</td>
<td>63.20</td>
<td>23.10</td>
<td>23.70</td>
</tr>
<tr>
<td></td>
<td>± 6.76</td>
<td>7.59</td>
<td>8.99</td>
<td>5.49</td>
<td>6.91</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>71.17</td>
<td>66.60</td>
<td>63.82</td>
<td>22.33</td>
<td>23.17</td>
</tr>
<tr>
<td></td>
<td>± 5.61</td>
<td>7.81</td>
<td>11.73</td>
<td>4.94</td>
<td>6.77</td>
</tr>
</tbody>
</table>

*p < .05, **p < .01, ***p < .001

The data shown in Table 9.3 suggest that, in many cases, the gains made by post-intervention are maintained or perhaps even slightly improved on by the 6-month
follow-up. However, the fact that standard deviations also tended to rise at follow-up, particularly for the fatigue severity measures, is indicative that the improvements were not consistently made or maintained within groups. Baseline BDI scores were found to act as a significant covariate in the analysis of the general fatigue scores repeated over the three time-points. The doubly-multivariate repeated measures ANOVA, therefore, was carried out with BDI scores as a covariate, and no significant overall main effects for group $F(10,44)=1.75$, $p>.05$ or time $F(10,90)=1.65$, $p>.05$ were found, nor was there an overall group by time interaction $F(20,188)=1.04$, $p>.05$. This suggests that, as with the sleep-activity data, improvements at post-intervention were not maintained.

**General Symptom Measures**

Examination of the data presented in Table 9.4 with respect to the general symptom variables reveals no clear patterns with respect to changes in the three scales over the three time-points of the study. This is reflected in the statistical findings, with no significant overall group $F(6,48)=1.04$, $p>.05$ or time $F(6,98)=0.68$, $p>.05$ main effects, and no significant interaction $F(12,150)=1.00$, $p>.05$. The small but significant improvements in POMS Confusion scores at Post-Intervention were neither significantly improved upon nor maintained at 6-month follow-up.
Table 9.4.

Means and standard deviations for the outcome measures of General Symptoms for each of the three intervention groups at pre- and post-intervention and follow-up.

<table>
<thead>
<tr>
<th></th>
<th>SF-36 Physical Functioning Scale</th>
<th>SF-36 Bodily Pain Scale</th>
<th>POMS Confusion Subscale</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Follow</td>
</tr>
<tr>
<td>CBT + Light</td>
<td>M</td>
<td>21.00</td>
<td>28.00</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>21.45</td>
<td>26.16</td>
</tr>
<tr>
<td>CBT + Placebo</td>
<td>M</td>
<td>33.00</td>
<td>34.00</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>19.75</td>
<td>22.09</td>
</tr>
<tr>
<td>Placebo Light</td>
<td>M</td>
<td>46.50</td>
<td>51.50</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>18.57</td>
<td>20.15</td>
</tr>
<tr>
<td>Total</td>
<td>M</td>
<td>36.83</td>
<td>41.17</td>
</tr>
<tr>
<td></td>
<td>SD</td>
<td>20.49</td>
<td>25.18</td>
</tr>
</tbody>
</table>

*p < .05 ** p < .01 *** p < .001

General Impairment Measures

Means presented in Table 9.5 demonstrate general improvements over time on all three scales for the CBT+Placebo and the Light Only groups. The CBT +Light group showed the same trend for SF-36 Role Functioning (Physical) Scale scores, but not for the other two scales, although SF-36 Social Functioning Scale scores remained higher at follow-up compared to baseline. Doubly-multivariate repeated measures ANOVA found no
Table 9.5.  
Means and standard deviations for the outcome measures of General Impairment for each of the three intervention groups at pre- and post-intervention and follow-up.

<table>
<thead>
<tr>
<th></th>
<th>SF-36 Role Functioning (Physical) Scale</th>
<th>SF-36 Role Functioning (Emotional) Scale</th>
<th>SF-36 Social Functioning Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Follow</td>
</tr>
<tr>
<td>CBT</td>
<td>M</td>
<td>3.75</td>
<td>5.00</td>
</tr>
<tr>
<td>Light</td>
<td>SD</td>
<td>0.00</td>
<td>8.44</td>
</tr>
<tr>
<td>Placebo</td>
<td>M</td>
<td>6.25</td>
<td>10.00</td>
</tr>
<tr>
<td>Light</td>
<td>SD</td>
<td>13.59</td>
<td>17.48</td>
</tr>
</tbody>
</table>

Total M 2.08 8.75 ++ 15.62 ++ 73.33 84.44 80.95 27.07 38.33 ++ 41.79 ++
Total SD 8.10 13.19 ++ 17.55 38.56 35.81 35.63 20.79 22.60 23.74

*p<.05 **p<.01 ***p<.001

Overall group by time interaction F(12,150)=1.47, p>.05 and no overall main effect for group F(6,48)=1.5, p>.05. A significant multivariate main effect for time was present F(6,98)=3.32, p<.01, and univariate repeated measures ANOVAs for the three DVs collapsed across groups found a significant increase in both SF-36 Role Functioning (Physical) Scale F(2,50)=11.21, p<.001 and SF-36 Social Functioning Scale scores F(2,50)=3.80, p<.05. Further comparisons of the significance of changes at each time point for SF-36 Role Functioning (Physical) Scale scores found significant improvements between pre-and post-intervention F(1,29)=12.71, p<.01, and pre-intervention and follow-up F(1,29)=12.42, p<.01, but the improvement between post-
intervention and follow-up did not attain significance $F(1,27)=3.34$, $p>.05$. The same analyses for the SF-36 Social Functioning Scale scores found significant improvements between pre- and post-intervention $F(1,29)=10.11$, $p<.01$, and pre-intervention and follow-up $F(1,29)=4.78$, $p<.05$, but no significant change between post-intervention and follow-up $F(1,27)=0.23$, $p>.05$.

**General Health Measures**

**Table 9.6.**

**Means and standard deviations for the outcome measures of General Health for each of the three intervention groups at pre- and post-intervention and follow-up.**

<table>
<thead>
<tr>
<th></th>
<th>SF-36 General Health</th>
<th>SF-36 Health Transition</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
</tr>
<tr>
<td><strong>CBT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>27.40</td>
<td>33.90</td>
</tr>
<tr>
<td>SD</td>
<td>18.11</td>
<td>17.39</td>
</tr>
<tr>
<td><strong>Light</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBT</td>
<td>21.50</td>
<td>25.90</td>
</tr>
<tr>
<td>M</td>
<td>10.01</td>
<td>14.08</td>
</tr>
<tr>
<td>SD</td>
<td>16.12</td>
<td>10.90</td>
</tr>
<tr>
<td><strong>Placebo</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>M</td>
<td>32.90</td>
<td>40.30</td>
</tr>
<tr>
<td>SD</td>
<td>15.36</td>
<td>15.11</td>
</tr>
</tbody>
</table>

*p <.05  **p <.01  ***p <.001
Table 9.6 suggests general small improvements across the three time-points for the treatment groups on both measures of general health, the only exception being a drop between post-intervention and follow-up in SF-36 General Health Perceptions Scale scores in the CBT+Light group. Baseline BDI score acted as a significant covariate in the doubly-multivariate repeated measures ANOVA $F(4,96)=3.10, p<.05$ and was, therefore, included in the analyses of these scales. Results indicated no overall group by time interaction $F(8,96)=0.74, p>.05$, and no overall main effects for group $F(4,50)=0.73, p>.05$ or time $F(4,96)=1.98, p>.05$.

**General Psychological Measures**

The most obvious characteristic of the data depicted in Table 9.7 is that the Light-Only group appear to score consistently lower than the other two treatment groups on all three measures of general psychological functioning at all three times. Doubly-multivariate repeated measures ANOVA found a significant overall main effect for group $F(6,48)=3.23, p<.05$, and follow-up univariate ANOVAs indicated that BDI scores collapsed across the three time-points differed between groups $F(2,25)=7.59, p<.01$. Scores were significantly lower for the Light Only group compared to the CBT+Placebo group ($p<.05$). No significant effects were detected for the POMS Depression $F(2,25)=1.98, p>.05$ or Anxiety $F(2,25)=1.13, p>.05$ subscales.
Table 9.7.
Means and standard deviations for the outcome measures of General Psychological Functioning for each of the three intervention groups at pre- and post-intervention and follow-up.

<table>
<thead>
<tr>
<th></th>
<th>Beck Depression Inventory</th>
<th>POMS Depression</th>
<th>POMS Anxiety</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre</td>
<td>Post</td>
<td>Follow</td>
</tr>
<tr>
<td>CBT M</td>
<td>11.80</td>
<td>10.70</td>
<td>8.20</td>
</tr>
<tr>
<td>+ SD</td>
<td>4.89</td>
<td>4.85</td>
<td>7.18</td>
</tr>
<tr>
<td>Light CBT M</td>
<td>14.90</td>
<td>14.20</td>
<td>9.00</td>
</tr>
<tr>
<td>+ SD</td>
<td>7.09</td>
<td>7.58</td>
<td>8.57</td>
</tr>
<tr>
<td>Placebo M</td>
<td>8.10</td>
<td>6.90</td>
<td>4.40</td>
</tr>
<tr>
<td>Light SD</td>
<td>4.33</td>
<td>2.77</td>
<td>1.43</td>
</tr>
<tr>
<td>Total M</td>
<td>11.60</td>
<td>10.60</td>
<td>7.07</td>
</tr>
<tr>
<td>SD</td>
<td>6.07</td>
<td>6.06</td>
<td>6.41</td>
</tr>
</tbody>
</table>

*p < .05  **p < .01  ***p < .001

No significant overall group by time interaction was present, $F(12,150)=0.38$, $p>.05$, however a significant overall main effect for time was found $F(6,98)=2.33$, $p<.05$. This effect was the result of a reduction in BDI scores across the groups over time $F(1,25)=7.41$, $p<.05$. Follow-up analyses to determine the timing of these reductions found no change between pre- and post-intervention $F(1,29)=1.52$, $p>.05$, while reductions between pre-intervention and follow-up $F(1,29)=7.41$, $p<.05$ and between post-intervention and follow-up $F(1,27)=5.21$, $p<.05$ were both significant. Reductions in POMS Depression $F(1,25)=1.65$, $p>.05$ and Anxiety sub-scales were not significant $F(1,25)=1.1$, $p>.05$. 
Discussion

The aims of this follow-up study were three-fold. The first aim was to assess whether the significant gains made by patients between pre- and post-intervention would be maintained at six-months from baseline. The second aim was to investigate whether other, more gradual changes in symptomatology and functioning might occur following treatment. The third aim was to examine whether the three treatment modalities would demonstrate differences in their efficacy overall and/or with respect to particular aspects of CFS patients’ symptoms and functioning.

With respect to the third aim, the lack of group by time interactions on any of the general areas of symptoms and functioning suggest that none of the treatment modalities could be said to have been any more effective than the others on any of the outcome measures. With respect to the second aim, the only significant change that occurred between post-intervention and follow-up was a general improvement in BDI scores across treatments. Although the significant improvements with respect to fatigue severity and responsiveness to sleep and/or rest that had been noted immediately post-treatment appeared to be maintained at the 6-month follow-up, variability in results meant that the improvement was no longer significant. This may be a reflection of the natural course of CFS, in that some participants appeared to have improved significantly
over the intervening period, while others may have lost treatment gains in fatigue levels or even deteriorated slightly. Sample-wide reductions in impairment with respect to physical and social functioning were, however, maintained.

It is clear, however, that the treatments did not lead to significant long-term improvements in symptomatology, as has been demonstrated to be the case for other behavioural interventions (Deale et al., 1998; Fulcher & White, 1997; Sharpe et al., 1996 Wearden et al., 1998). As discussed in the previous chapter, this can be explained in part by the differences in protocols in terms of intensity and duration of treatment and the fact that, on average, patients from the current study had suffered from the illness for more than twice the duration of participants in the other trials. Another important reason for the lack of long-term effects is that once the light-exposure sessions are finished, the most potent zeitgeber for the circadian system is removed. Unless patients remain vigilant with respect to the regularity of their sleep-activity schedules and/or ensure adequate exposure to natural light, rhythms can easily dissociate again.

In the absence of a placebo or no treatment comparison group, it is not possible to attribute any of the few changes that were maintained or took place following intervention to the treatment process itself. The improvements noted in depression scores and maintenance of improved social and physical functioning could reflect a general treatment response, although they may just as well have resulted from a natural
improvement in symptomatology over time, or perhaps an increase in adaptation to the illness.

On the other hand, anecdotal reports (written on a blank section of the questionnaire where participants were invited to comment on any aspect of the study) from a number of the participants involved in the study suggest that, while the treatment protocols may not have made a substantial impact upon symptomatology, they may have been instrumental in assisting patients to take a more adaptive approach to their illness. At the 6-month follow-up, two patients had returned to full-time work, one of whom, an accountant, had not worked professionally for more than 10 years. Another 5 patients had taken up either part-time work or study, and two others had made significant lifestyle changes, one with respect to their living arrangements while the other implemented a major career change. All of these changes were seen as highly positive, and participants indicated that the treatment that they had received as a result of their involvement in the study had been, to varying extents, important in assisting them to design and implement such changes.

Almost exclusively, participants cited the cognitive, rather than circadian aspects of treatment as being instrumental in this process, and indicated that the main effect had been an alteration in the way that they viewed their illness and their level of control over symptoms. These kinds of changes may, therefore, have been responsible for the improvement in depression scores between post-treatment and follow-up, and the
maintenance of increased physical and social functioning. While this provides no evidence in support of circadian intervention in CFS, such a process would be consistent with the results of the major CBT trials that have been previously reported (Deale et al., 1998; Sharpe et al., 1996) and, as such, offer further support for the utility of that treatment strategy.
CHAPTER 10

GENERAL DISCUSSION AND CONCLUSIONS
**Introduction**

Chronic fatigue syndrome is an enigmatic diagnostic entity that has proved to be one of the more persistent medical conundrums over the last century, and probably longer, with recognisable descriptions dating back to the middle of the 18th century (Demitrack & Abbey, 1996). Elusive in historical as well as scientific terms, the diagnosis has changed both name and, to some extent, form a number of times since the original description of Neurasthenia by Beard (1869) and Van Deusen (1869). Nevertheless, the common threads of the disorder, characterised by unexplained debilitating fatigue accompanied by cognitive and various other somatic symptoms, can be traced through a series of unexplained medical syndromes that have been reported through the 20th century.

Despite a substantial international research effort, which has become considerably more focused in the last two decades, the aetiology and pathophysiology of the disorder are still not well understood. CFS has, so far, eluded conceptualisations as a disorder primarily related to infection, disturbed immunity, neuroendocrine dysfunction, sleep disturbance or psychiatric illness (Wessely et al., 1998). However, despite the inability of these approaches to, in their own right, account for the presence and persistence of all cases of CFS, empirical evidence has accrued to suggest that each of them may play some role in the aetiology and maintenance of at least some cases of the illness (Demitrack, 1996). As a result, CFS is now viewed more as a clinical condition, rather
than as a discrete disease process, in which various environmental, psychological and physiological factors interact to produce the symptom complex (Demitrack & Abbey, 1996). In this context, it is clear that the task of investigating the nature of the illness demands a biosocial approach, which allows for the integration of the study of the various physiological, psychological and social factors that are thought to contribute to the disorder.

The aim of this thesis was to conduct a series of studies to investigate whether circadian dysregulation could be one of the factors that contributes to the overall processes that lead to and maintain CFS. A circadian approach fits well within an over-arching biosocial conceptualisation of CFS, due to the fact that the regulation of the circadian system entails the temporal coordination of an individual's physiology, behaviour and physical and social environments (Turek, 1994). The specific rationale for the study of circadian factors in CFS was based primarily upon the relevance of circadian integrity to the proper functioning of many of the physiological and behavioural systems (e.g. immune, neuroendocrine, sleep-wake) that previous research has indicated to be dysregulated in CFS patients (Moldofsky, 1993;1995). Recent empirical studies have provided evidence of the presence of physiological circadian dysregulation in CFS patients (Williams et al., 1996). Almost simultaneously, the HPA abnormalities that have been described in CFS (Demitrack et al., 1991) have been reported to occur in people whose circadian functioning was behaviourally compromised, namely shift-workers (Lecce et al., 1996).
A series of studies was therefore undertaken to investigate the behavioural and physiological integrity of the circadian systems of CFS patients. The main questions that these studies sought to investigate were whether CFS was associated with circadian dysregulation in general, and states of external and/or internal circadian desynchrony in particular. The rationale for investigating CFS patients for external desynchrony followed from the Leese et al. (1996) study of CFS-like HPA-axis abnormalities in shift-workers, given that shift-work is intrinsically associated with states of external desynchrony. The rationale for testing for internal desynchrony was based on evidence that sleep-wake/SCN desynchrony engenders a state of internal temporal dysregulation (Turek, 1984) that can produce disturbances similar in nature to those associated with the core symptomatology of CFS (Boivin et al., 1997; Dijk et al., 1992; Van Cauter, 1990). Studies 1 to 3, which examined behavioural and physiological rhythms in CFS patients compared to healthy controls, were specifically aimed at investigating these issues.

A secondary aim of the thesis was to examine any significant circadian abnormalities found in CFS patients in order to establish their clinical significance. While Studies 1 and 3 included preliminary attempts to assess whether relationships between symptom measures and circadian functioning were present, Studies 4 and 5 employed a prospective methodology in an attempt to investigate the causal nature of these relationships.
This chapter will first summarise the findings of the five studies, and then discuss what conclusions may be reasonably drawn with respect to the presence, cause, and clinical significance of circadian dysregulation in people with CFS. Finally, the major implications of these findings with respect to the continued study of CFS will be discussed.

**Summary of Results of Studies 1-5**

**Study 1**

Study 1 was undertaken in order to investigate whether the sleep-activity patterns of CFS sufferers differed systematically from those of healthy individuals. Thirty-two CFS patients and the same number of controls matched for age, sex and work status self-monitored their normal sleep-activity patterns for 14 days. Compared to the healthy controls, the sleep-activity rhythms of CFS participants were characterised by lower overall activity levels, reduced amplitude, and a phase delay of around 45 minutes. While CFS participants were more heterogeneous, as a group, with respect to the timing of their sleep-activity patterns, there was no evidence that, as individuals, they were less regular from day to day. With respect to sleep itself, CFS and control groups slept for
the same amount of time each day, although the CFS group showed significantly longer sleep-onset latencies and poorer sleep efficiency, and these findings closely replicate those of Sharpely et al. (1992). While reduced sleep efficiency was not significantly correlated with altered sleep-activity rhythm parameters, longer sleep-onset latencies were related to reduced sleep activity mesor and amplitude. Lower scores on the subjective physical well-being measure were also related to longer sleep-onset latencies and reduced amplitude of the sleep-activity rhythm.

These findings offered some evidence that disturbances to the sleep-activity rhythm could be related to disturbances of sleep and well-being in CFS patients, although they provided no clue as to the causal nature of this relationship. It was hypothesised, however, that the delay in CFS sleep-activity patterns, and longer sleep-onset latencies, could have been related to an underlying delay in physiological timing. It was speculated that such a physiological delay may have been produced by a partial free-run of the SCN rhythm, which was, in turn, due to a reduction in non-photic entrainment cues as a result of reduced sleep-activity rhythm amplitude.

**Study 2**

Study 2 was undertaken to examine the relationship between sleep-activity patterns and the timing of the endogenous clock, using core temperature as an indicator
rhythm. Twelve CFS participants were compared with age- and sex-matched healthy controls in their normal environments and, again, they demonstrated lower activity levels and reduced amplitude of the sleep-activity rhythm. However, in contrast to the results of Study 1, no evidence of an overall phase delay in the timing of sleep-activity patterns was found. The 72 hours of core temperature monitoring found no between group differences on any of the rhythm parameters tested, including mesor, phase, amplitude and goodness of fit to a cosine function with a 24-hour period. There was also no evidence of instability in the timing of core temperature rhythms in the CFS group across the three days. The relationship between the timing of sleep-activity and core temperature rhythms appeared to be weaker in the CFS group, although this was only significant when the temperature data were subjected to the purification by intercepts method.

Thus, although these results provided some support for the hypothesis that CFS is associated with a degree of behavioural and physiological circadian dysregulation, they offered no support for the existence of the underlying phase delay in physiological timing that was hypothesised in Study 1. However, a lack of power due to low participant numbers and a lack of environmental controls limited any conclusions that could be drawn.
Study 3

A larger laboratory based study was, therefore, implemented in an attempt to resolve the differences between the first two studies and to replicate the Study 2 finding of a weaker association between sleep-wake and core temperature rhythms in CFS participants. This study also sought to further investigate the relationships between circadian functioning and the symptomatology of CFS. In Study 3, the circadian functioning of a group of 19 CFS participants was compared with that of 19 age- and sex-matched healthy controls. The protocol under which core temperature monitoring was carried out meant that potentially confounding factors, such as light exposure, ambient temperature, physical activity, sleep, and meal timing were controlled for.

As in the two previous studies, CFS participants displayed lower activity levels and reduced amplitude of the sleep-activity rhythm in the two weeks prior to temperature monitoring. As was the case in Study 1, the sleep-activity rhythms of the CFS group were also phase delayed by just over an hour relative to controls, and the timing of the nocturnal sleep period was significantly more variable. Core temperature rhythms differed between groups only with respect to timing, with those of the CFS group being delayed by around an hour and a half relative to those of the controls. This finding was consistent with the suggestion arising out of Study 1, that the delay in sleep-activity timing and increased sleep-onset latencies could be indicative of an underlying delay in physiological timing.
Correlation coefficients assessing the relationship between the endogenously driven component of the core temperature rhythm and sleep-wake were consistently lower for the CFS group although, as was the case in Study 2, the differences only attained significance when the method of purification by intercepts was used to unmask the temperature data. Further exploratory analyses in Study 3 found significant relationships between measures reflecting the salience of the core temperature rhythm (amplitude and goodness of fit) and symptom variables (self-reported number of somatic symptoms and fatigue levels) suggested a link between circadian dysregulation and CFS symptomatology, although they did not inform as to its clinical significance.

**Studies 4 and 5**

Studies 4 and 5 attempted to prospectively ascertain the clinical significance of circadian dysregulation in CFS via the use of a placebo controlled treatment trial. Study 4 examined the impact on symptomatology of treatments designed to restore circadian integrity. These treatments entailed the use of appropriately timed bright light exposure alone or in combination with behavioural programs designed to regularize and consolidate the sleep-activity cycle. The thirty patients enrolled in the therapeutic groups demonstrated clinically modest but statistically significant gains across a number of outcome measures, however, these were almost entirely matched by improvements
experienced by participants exposed only to the placebo condition. The only significant
differences between the groups were with respect to a greater decline in fatigue levels
and an increase in the responsiveness of fatigue to sleep and/or rest in the treatment
compared with placebo groups. Again, these improvements were small in magnitude
and of uncertain clinical value. Nevertheless, they did correlate with variables indicative
of improved salience of the sleep-activity rhythm, which was a specific goal of
treatment.

Study 5, a 6-month follow-up, indicated that almost all of these treatment gains had
diminished over time. Those improvements that were maintained were suggestive of
improved adaptation to the illness, rather than any substantial reduction in
symptomatology. However, even these improvements cannot be attributed to circadian
intervention *per se*, in that they were more likely to have arisen from cognitive aspects
of the programs, or may simply have been part of the natural process of adapting to the
illness over time.

**Conclusions Regarding Circadian Integrity in CFS**

It is suggested that several conclusions about the circadian functioning of CFS patients
can be drawn from the combination of findings from the studies summarised above.
These are divided into four general areas, in line with the general hypotheses put

**Salience of the sleep-activity rhythm**

As expected, the first three studies found lower activity levels and reduced amplitude of the sleep-activity rhythm in CFS groups, compared with control groups. Reductions in activity levels are a natural consequence of many states of ill-health, but particularly in an illness such as CFS, where physical and mental activity are both reported to exacerbate and be limited by symptomatology (Farrar, Locke & Kantrowitz, 1995). Reduced amplitude of the sleep-activity rhythm could have been expected purely as a consequence of reduced activity levels. However, the findings of reduced nocturnal sleep efficiency and increased day-time napping in Study 1 indicate that the natural sleeping-waking rhythm is less consolidated in CFS patients and this would also have contributed to reduced sleep-activity rhythm amplitude. Given the strength and consistency of the findings of Studies 1-3, it can be concluded that the sleep-activity rhythms of CFS patients are, in general, less salient than those of healthy individuals.

To the best of the author’s knowledge, these are the first investigations of sleep-activity rhythms in CFS patients. Reduced rest-activity rhythm mesor and amplitude has been reported in other populations, including: adults with major depression (Raoux, Benoit &
Dantchev, 1994; von Zerssen et al., 1985), children with seasonal affective disorder (SAD: Glod, Teicher, Polcari, McGreenery & Ito, 1997), and demented and non-demented elderly people (Pollack & Stokes, 1997). Also, Teicher, Glod and Magnus (1997) reported reduced rest-activity rhythm mesor, but normal amplitude, in adults with SAD.

**External Synchrony**

The findings with respect to phase of sleep-activity rhythms were less consistent, with the results of Studies 1 and 3 indicating significant delays (44 and 62 minutes, respectively) for the CFS groups, while the acrophases of sleep-activity of CFS patients and Controls tested in Study 2 were no different. The core temperature rhythms of CFS participants in Study 3 were delayed by approximately 90 minutes, while those of the Study 2 CFS group were actually non-significantly advanced, by approximately 60 minutes. Several factors are likely to have contributed to this inconsistency. First is the fact that Study 2 had a substantially smaller number of participants (n=22) compared to Studies 1 and 3 (n=64 and 38 respectively) and was, therefore, more prone to the vagaries associated with sampling error. A second factor that must be considered is that the terms ‘advance’ and ‘delay’ are somewhat arbitrary in that they are based on the phase of one rhythm relative to another (in this case core temperature relative to the ambient light-dark cycle) at a particular moment in time, and do not reflect the process
by which the phase relationship came about. Because the functions being measured are
cyclical, an apparent two-hour phase advance of one rhythm (Rhythm A) relative to
another (Rhythm B) at any given moment could just as well be described as a 22-hour
phase delay. The validity of the descriptor applied would depend on whether the phase
relationship of the two rhythms had come about because Rhythm A had been cycling
over a shorter period than Rhythm B (phase advancing) or, in the opposite situation,
where Rhythm A had been cycling over a longer period so that it had almost ‘caught up’
to Rhythm B again (phase delaying). This opens the possibility that some extreme cases
of phase delays were erroneously regarded as phase advances (or vice versa) due to the
procedures employed in operationalising and analysing the data.

However, both of the above explanations as to why the data from the three studies were
inconsistent are weakened by the fact that standard deviations associated with mean
phase measures were similar across all studies. Although it would not always be the
case, one would expect that if either sampling error or misclassification of phase
relationships were prominent factors in producing inconsistent findings, then measures
of inter-individual variability for Study 2, in particular, would be somewhat higher than
for the other studies. It is perhaps more reasonable to conclude, therefore, that although
CFS patients often display a degree of external desynchrony in the form of a phase delay
of both behavioural and physiological timing, the inherent heterogeneity that has often
been noted in sufferers of the syndrome (Demitrack & Abbey, 1996; Wessely et al.,
1998) is also evident in this regard.
Again, the only comparable findings from past research come from the literature dealing with rhythm alterations on affective disturbances. Teicher et al. (1997) reported phase delays of rest-activity of similar magnitude to those found in Studies 1 and 3 in their group of adult SAD patients. Another study of SAD also reported significant phase delays of core temperature and cortisol rhythms (Avery et al., 1997). On the other hand, phase advances of physiological timing have been reported in patients with major depression (Kupfer, Foster, Coble, McPartland & Ulrich, 1978), although this finding has not been consistently replicated (Munk et al., 1994). More recent work suggests that the fundamental rhythm disturbance in major depression is one of phase variability rather than a phase shift (Daimon et al., 1992).

**Internal Synchrony**

Studies 2 and 3 examined the strength of the relationship between the sleep-wake cycle and core temperature rhythms in CFS patients and healthy controls. Both studies found that correlation coefficients describing the relationship were consistently lower for the CFS group, regardless of whether the temperature data were raw or purified. In both studies, however, the difference between group correlation coefficients was statistically significant only when the purification by intercepts method (Waterhouse et al., 1999) was employed. Nevertheless, strong trends in the same direction were evident when
alternative purification methods were used, and it is suggested that the lack of
significance was the result of reduced sensitivity of the protocols due to the likelihood
that these methods were less effective at demasking the endogenous component of the
core temperature rhythm. Discussion as to why purification by 16 categories
(Waterhouse et al., 1999) and correction for sleep (Carrier & Monk, 1997) methods may
have been less effective than purification by intercepts (Waterhouse et al., 1999) was
presented in detail in the discussion of Studies 2 and 3.

The findings of Studies 2 and 3 suggest that the sleep-wake cycles of people with CFS
are less effectively synchronised with the endogenous rhythm of core temperature. This
is consistent with the findings of Williams et al. (1996) in which CFS patients, compared
with healthy controls, demonstrated a weaker relationship between the timing of core
temperature and melatonin rhythms. Taken together, the results of the current series of
studies and Williams et al. (1996) suggest that CFS is associated with a degree of
internal circadian desynchrony. A weakening in the coupling of internal rhythms has
also been suggested to be the fundamental rhythm disturbance that exists in patients
suffering from major depression (Daimon et al., 1992). The parallels between CFS and
rhythm affective illness with respect to rhythm disturbances will be discussed in the final
section of this chapter.
Clinical Significance of Circadian Dysregulation in CFS

The findings of the studies reported in this thesis indicate that there is a relationship between the symptomatology of CFS and aspects of circadian functioning. Study 1 noted relationships between poorer physical well-being, increased sleep-onset latencies, and reductions in sleep-activity rhythm amplitude. It was suggested that increased sleep-onset latencies may be the result of a relative phase delay in the SCN rhythm brought about by a lack of exposure to photic and non-photonic time-cues. However, it could not be determined whether poorer physical well-being was a cause or an effect of reduced rhythm amplitude, increased sleep-onset latencies or the hypothesised phase delay.

The idea that a phase delay of physiological rhythms relative to sleep-activity was related to increased symptomatology was supported by the fact that healthy controls in Study 3 showed reduced vigour and increased confusion scores as core temperature rhythms delayed relative to sleep-wake. Paradoxically, however, the data from the CFS group in the same study directly conflicted with control findings, in that phase delays of the core temperature rhythm were related to increased vigour and reduced confusion. Another puzzling finding from this study was that, although reduced amplitude of the core temperature rhythm was associated with increases in the number of somatic symptoms and fatigue reported by CFS participants, core temperature amplitude was not significantly lower in CFS patients compared with controls.
Perplexing as these findings may have been, they were at least indicative of an association between circadian parameters and the symptomatology of CFS. However, conclusions as to the causal nature of these relationships could not be made on the basis of cross-sectional investigations. It was therefore unclear as to whether circadian dysregulation was: a) an active component in the central pathology of CFS; b) yet another symptom of the syndrome, perhaps contributing to the occurrence and or maintenance of a number of other secondary symptoms or; c) a mere epiphenomenon of the disorder of no clinical significance.

Studies 4 and 5 represented an effort to investigate this issue prospectively, by conducting a placebo controlled trial of the effects of treatments designed to improve circadian regulation in CFS sufferers. As reported, the use of bright light and behavioural interventions alone and in combination failed to produce the type of substantial clinical improvements that would be expected if circadian factors played a major role in the underlying pathology of CFS. The possibility that circadian factors might nevertheless contribute to symptomatology to some degree was supported by the small but significant improvements noted in fatigue levels and their responsiveness to sleep, and the fact that these were related to improvements in the amplitude and goodness of fit of the sleep-activity rhythm.

The fact that circadian intervention did not significantly outperform the placebo condition, even when complimented by the addition of cognitive-behavioural
components, compares rather poorly with the results of recent controlled treatment trials that have assessed the efficacy of CBT. Sharpe et al. (1996) and Deale et al. (1997) both reported that substantial gains were made with respect to the health status and functional capacity of their patients. However, these protocols were substantially longer than the current one, and were conducted with patients who had suffered from CFS for a shorter time. Another placebo controlled trial of CBT in CFS, which was of similar duration and conducted with a patient group of similar average length of illness, also failed to show any benefit of CBT (Lloyd et al., 1993). It was also pointed out in Chapter 8 that, due to practical limitations, an assessment of whether intervention actually resulted in the full or partial restoration of circadian integrity in patients could not be established.

As such, it is possible that the protocols used in the current study were not substantial enough in terms of duration or intensity to produce treatment effects that were statistically as well as clinically significant. On the basis of current information, therefore, it can only be concluded that while circadian dysregulation appears to be associated with some of the symptoms of CFS, there is no evidence that it plays a major role in their generation and/or maintenance. Improvements in fatigue in association with improvements in measures reflecting the salience of the sleep-activity rhythm are consistent with the possibility that circadian dysregulation may be a peripheral but significant contributor to symptom severity.
A Theoretical Model of Circadian Dysregulation in CFS

On the basis of the findings of the Studies 1-5, a hypothetical model of the role of circadian dysregulation is proposed (Figure 10.1). In the absence of evidence suggesting that circadian dysregulation plays a central role in the pathology of CFS, the model assumes that it is one of the many perpetuating factors.

The model posits that reduced activity levels are a natural consequence of the symptoms such as fatigue and pain in particular, or the threat of their exacerbation. Inactivity through the day combines with nocturnal sleep disturbance and daytime napping behaviour to reduce the salience of the sleep-activity rhythm. Given that exposure to a salient light-dark cycle is also likely to be limited by the nature of the illness, the circadian systems of sufferers would have fewer cues with which to entrain to the ambient light-dark and social cycles of their environments. It is likely that, in most cases, fewer (as opposed to no) environmental time-cues mean that entrainment is not lost altogether, but is more loosely maintained.

As the natural period of the SCN rhythm is slightly longer than 24 hours, the most probable outcome of weaker entrainment to the environmental cycle is a phase delay of physiological timing. This would generally result in a tendency for behavioural rhythms to also phase delay, as the physiological drive for sleep and wakefulness would occur later each day. However, as suggested by the sleep profiles of CFS patients in Study 1,
Figure 10.1 Theoretical model of the relevance of circadian dysregulation in CFS. Predisposing, precipitating and perpetuating factors are as for Demitrack (1996: see Chapter 3), however, the generation and effect of circadian dysregulation is elaborated (shaded boxes). The model posits that circadian dysregulation, in the form of a weakening or loss of external and internal synchrony is due primarily to reduced salience of sleep-activity rhythms as a result of inactivity and sleep-disturbance. Circadian dysregulation then contributes to the syndrome as one of several perpetuating factors.
the individual may resist the physiological pressure to continually phase delay in an 
effort to maintain a normal social rhythm. Regardless, internal synchrony between 
sleep-wake and the rhythm of the SCN is likely to be compromised to some extent, 
resulting in a degree of internal temporal disorganisation.

This process may explain the lack of temporal association between core temperature and 
melatonin rhythms noted in CFS patients by Williams et al. (1996). Such a process may 
also contribute to HPA axis abnormalities associated with CFS (Demitrack et al., 1991), 
given that Leese et al. (1996) demonstrated that similar abnormalities occurred in 
healthy people as a result of circadian dysregulation associated with shift work. Further, 
even a mild degree of chronic internal temporal disorganisation is unlikely to help the 
systems of CFS sufferers to cope with whatever other pathological processes contribute 
to the disorder, and could clearly contribute to symptoms such as sleep disturbance. As 
Moldofsky (1993; 1994; 1995) has repeatedly pointed out, disturbances to the sleeping-
waking brain invariably lead to disturbances in other areas, including immune and 
neuroendocrine functioning.

While the model presented in Figure 10.1 attempts only to describe a single aspect of the 
multifaceted process by which CFS is generated and maintained, it provides a 
framework through which various hypotheses with respect to circadian dysregulation in 
CFS can be generated, tested and further explained.
Implications of Findings to the Ongoing Study of CFS

Clearly, further work is required to establish whether the model proposed above provides an accurate conceptualisation of the general relationship between circadian dysregulation and CFS. Nevertheless, it provides a context from within which to interpret the findings of the current series of studies, and the others that have investigated circadian factors in CFS (Hamilos et al., 1998; Leese et al., 1996; MacHale et al., 1998; van der Luit et al., 1998; Williams et al., 1996; Wood et al., 1998).

While the model posits that circadian dysregulation is secondary to whatever pathological processes may underpin CFS, the possibility that circadian factors may play a more central role cannot be completely dismissed. The current series of studies examined circadian regulation at a general level, and it is conceivable that abnormal entrainment or altered circadian expression of a specific physiological factor or group of factors may demonstrate a more direct relationship to symptomatology. The most obvious candidate for investigation in this respect would be the component rhythms of the HPA axis, although, given the limitations of current techniques, the monitoring of hormones such as CRH and vasopressin, which are both released and act within the brain, is so impractical as to be considered impossible in humans. Studies that carefully obtain complete circadian profiles of ACTH and cortisol secretion in CFS patients, while controlling for differences in sleep-wake timing, may nevertheless provide useful information in this regard.
Given the various and substantial practical difficulties associated with obtaining numerous repeated blood or saliva samples from a reasonable number of people under tightly controlled conditions and over an extended period of time, it would be most efficient to sample a number of parameters simultaneously. A particularly powerful protocol would entail at least hourly blood/saliva and temperature sampling over at least a 36-hour period in groups of CFS patients, healthy controls, and a second patient group, such as sufferers of major depression. Blood/saliva samples could then be assayed for cortisol, ACTH and melatonin, and data could be analysed with respect to the synchrony between the various rhythms (sleep-wake, melatonin, cortisol, ACTH and core temperature), as well as the other circadian parameters (amplitude, mesor, frequency, goodness of fit). Such a protocol would also allow for a more definitive assessment of the hypothesised presence of hypocortisolaemia in CFS, in that levels could be averaged across a complete circadian cycle, thus eliminating phase alterations as a nuisance variable. Indications as to the nature of the association between circadian abnormalities and symptomatology may be obtained by carrying out such a procedure in a CFS group during relapses and again during times when they report feeling relatively well.

Overall, the findings of the studies contained in this thesis are consistent with the proposition put forward by Moldofsky (1995) that CFS is associated with chronobiological dysregulation, although they do not clarify the extent to which chronobiological disturbance is a result of or contributes to the illness. Evidence of
phase alterations, increased variability, and weaker internal synchrony, combined with evidence from other work (Williams et al., 1996), suggests a scenario of general dysregulation of behavioural and physiological rhythms. The similarities of these findings with respect to those relating to SAD and major depression (Avery et al., 1997; Daimon et al., 1992; Glod et al., 1997; Teicher et al., 1997) inevitably raise the perennial issue of the relationship between CFS and affective disturbance.

However, the fact that depression was always controlled for in the analyses where it had a significant impact, suggests that the current findings are not an artefact of the high rates of comorbidity of CFS and affective illness. Further, while the most consistent finding with respect to circadian factors in depression is a reduction of the amplitude of physiological rhythms (Daimon et al., 1992), the CFS patients in the current studies did not demonstrate evidence of this. Even more contrasting are the findings of van der Luit et al. (1998) of increased amplitude of heart rate and systolic and diastolic blood pressure in their group of CFS patients. This led these investigators to hypothesise that CFS was associated with increased amplitudes of physiological rhythms (van der Luit et al., 1998).

The scenario of CFS being associated with increased circadian amplitudes, while depression is associated with decreases, parallels the suggestion that CFS and depression are associated with opposite extremes of plasma cortisol levels (Demitrack et al., 1991). However, it would seem unlikely that the amplitudes of all, or even many, physiological
parameters could be increased in CFS. Certainly, there was no evidence in the present series of studies to suggest that core temperature amplitudes were increased in CFS, and if anything, circadian dysregulation is more likely to lead to a dampening of most rhythms (Turek, 1994; Van Cauter, 1990).

While this may be further evidence that CFS and major depression both overlap with and are qualitatively different from each other, the parallels between the two conditions with respect to rhythm disturbances may not be particularly significant with respect to questions of shared aetiology or pathology. The integrity of circadian time-keeping has mostly been studied in relation to psychiatric and sleep disorders, and its presence and contribution in other states of ill-health is largely unknown. Clearly, the mechanisms hypothesised to generate and maintain circadian dysregulation in CFS in Figure 10.1 could generalise to many disease states. As such, the specificity of the current findings to CFS is unknown, as is the specificity of their comparability to depression.

Indeed, given the ubiquity of fatigue as a symptom, both in the general population (Loge et al., 1998) and in primary medical care settings (Hickie et al., 1996, Kroenke et al., 1988), and the overlap that the symptomatology of CFS shares with a wide range of other disorders, investigation of circadian functioning in other states of ill-health would appear to be warranted.
This raises an associated issue that treatment research in CFS needs to address. It is generally unclear whether improvements reported in treatment studies are due to a direct effect on the underlying pathology of the CFS, or to an improvement in patients' ability to adapt to that pathology. Using the current research as an example, previous reports of the general lack of exposure to a salient light dark cycle associated with life in the industrialised world (Savides et al., 1986) suggest that the sleep quality and general well-being of many people might improve somewhat if they were to undergo programs that increased circadian integrity. This question of treatment specificity could just as well be raised about the other treatment programs for CFS that have reported more substantial beneficial effects. The graded exercise program instituted by Fulcher and White (1997), for example, could be argued to be likely to lead to significant improvements in the health status of any individual who led a sedentary lifestyle. Even the investigations reporting substantial treatment effects through CBT noted that it was rare for any patients to become symptom free as a result of treatment (Deale et al., 1998; Sharpe et al., 1996). While this should not detract from the achievement of these studies in demonstrating that much of the disability associated with CFS is treatable, the question as to whether one is treating the underlying pathology, or simply improving a patient's ability to cope with it is an important one. This is particularly so when treatment trials, like the current one, are used as a method of investigating aetiology. Further research will, it is hoped, clarify such issues.
Regardless of their specificity, the findings detailed in this thesis have two major implications for the research and treatment of CFS. The first of these is that circadian abnormalities, whether or not they are secondary to the central pathology of CFS, may contribute to its expression via the exacerbation or maintenance of sleep, immune and neuroendocrine dysregulation. Although the preliminary attempt to intervene to correct circadian dysregulation described in Study 4 was unsuccessful at producing any clinically significant gains in CFS patients, the possibility remains that attention to circadian factors in the general treatment of CFS sufferers may improve overall treatment outcomes.

The second major implication is that altered circadian functioning, particularly with respect to circadian phase, has been and remains a significant potential source of error variance in studies that have investigated various aspects of physiology and behaviour of CFS patients without controlling for intra- and inter-group differences in sleep-wake habits. Moldofsky (1995) has previously suggested that the inconsistency of research findings that characterises the area is due, at least in part, to a lack of awareness of the influence that time of day and individual differences in circadian timing has on many of the parameters studied. The results of Studies 1-3 in particular, suggest that, at least, a basic assessment of sleep-wake patterns of CFS patients and controls should be made prior to sampling to ensure that data are collected at comparable circadian times.
With respect to the bigger picture, the findings reported in this thesis offer further support to the view that CFS is a complex condition resulting from the interaction of a number of diverse predisposing, precipitating and perpetuating factors (Demitrack & Abbey, 1996; Fox & Cleare, 1998; Hickie et al., 1995; Wessely et al., 1998). The complexity of this interaction is underlined by the fact that, although it may only be one of a number of factors that combine to perpetuate the condition, circadian dysregulation itself is the result of a complex interaction of behavioural, physiological, and environmental interactions. This further emphasises the assertion that there will be no simple answers with respect to CFS (Thomas, 1993), and the importance of a biosocial approach to the investigation and treatment of the condition.

On many levels, CFS is an extremely challenging condition, for patients, clinicians and researchers alike. Although the drive to elucidate the mechanisms that generate and maintain the symptom complex is likely to require a considerable and continuing effort, it is just as likely that the reward will entail a much deeper understanding of the processes that contribute to health and disease in general.
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APPENDIX A:

SEMI-STRUCTURED CLINICAL INTERVIEW FOR CFS
Structured Clinical Interview
For CFS

Date:

Code:

What was your date of birth?

What is the highest education level you have achieved so far?

What is your occupation?

What is your current work status?

1. Working or Studying
2. Not Working or Studying

If Working or Studying:

How many hours per week do you currently do?

1. Full-time
2. 30-40 hours
3. 20-29 hours
4. 10-20 hours
5. <10 hours

If Not Working

How are you currently being supported?

1. Unemployment benefits
2. Spouse
3. Parent
4. Other family
5. Savings
6. Other ____________
**Current Illness:**

When do you think your CFS began? That is, when did you first notice that something was wrong?

Approx. date of onset: ______________________

Time since contracting CFS: ______________________

When were you actually diagnosed as suffering from CFS?

Approx. Date: ______________________

Who made the CFS diagnosis?

1. General Practitioner
2. Specialist
3. Allied Health Professional
4. Alternative Practitioner
5. Other (specify): ______________________

Has the diagnosis been confirmed or challenged by another source since then?

YES  NO

By Whom?

1. General Practitioner
2. Specialist
3. Allied Health Professional
4. Alternative Practitioner
5. Other (specify) ______________________

Details: ____________________________________
**Current Symptoms:**

**Can you tell me about your current symptoms, that is those that you have been experiencing over the past month or so?**

Circle if symptoms are spontaneously reported, tick if reported following prompting:

1. FATIGUE  YES  NO
2. Significant memory/concentration deficits  YES  NO
3. Sore throat  YES  NO
4. Tender cervical or axillary lymph nodes  YES  NO
5. Muscle pain  YES  NO
6. Multi-joint pain (without swelling or redness)  YES  NO
7. Headaches (new type/pattern/ severity)  YES  NO
8. Unrefreshing Sleep  YES  NO
9. Post-exertional Malaise (lasting more than 24 hours)  YES  NO

Number of Concurrent Symptoms:  

Other symptoms reported:

Total number of symptoms reported: 

**What would you say was your most significant symptom?**

**How would you describe your fatigue?**  

<table>
<thead>
<tr>
<th>Not bad at all</th>
<th>Moderately bad</th>
<th>Severe</th>
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</table>
Is the fatigue you experience now like fatigue you had experienced before you contracted CFS?

**YES**

**NO**

How much of the time do you feel this fatigue?

1. All of the time
2. Most of the time
3. About half the time
4. Some of the time
5. Irregularly

What kinds of things exacerbate your symptoms?

What kinds of things relieve your symptoms?

Compared with other healthy people, how active in each of these areas would you say you were before you illness came about?

<table>
<thead>
<tr>
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<th>Not active at all</th>
<th>Average</th>
<th>Extremely active</th>
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<tr>
<td><strong>Occupationally</strong></td>
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<td><strong>Physically</strong></td>
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Compared with other healthy people, how active in each of those areas would you say are now?

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<th>Not active at all</th>
<th>Average</th>
<th>Extremely active</th>
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Did the symptoms originally come on over a period of:

1. Years  
2. Months  
3. Weeks  
4. Days  
5. Hours

Classify:

1. Sudden onset  
2. Insidious onset

What was your physical health like around the time immediately preceding the onset of your symptoms?

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<tr>
<th>Very Poor</th>
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<th>Perfect</th>
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Were you suffering from any specific medical illnesses?

Yes (what?)

No

What was your lifestyle like around the time immediately preceding the onset of your symptoms?

Were there any major events or upheavals in your life at that time, such as a change in the circumstances of your:

1. Work  
2. Education  
3. Family  
4. Relationships  
5. Place of living

How did you react to these:
How would you describe your psychological around the time immediately preceding the onset of your symptoms?

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<tr>
<th>Very Poor</th>
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Would you say that leading up to the illness you were...

**DEPRESSED?**

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**ANXIOUS?**

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**STRESSED?**

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**OTHER?**

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Classify circumstances preceding CFS onset:

1. Viral
2. Period of physical stress
3. Period of emotional stress
4. Unhealthy lifestyle
5. Other ________________________________
6. No clear antecedents
Note any evidence of psychomotor retardation: YES  NO

Which of the following best describes the pattern of your fatigue?

1. Persistent and severe
2. Persistent fatigue with relapses into severe fatigue
3. Periods of normal functioning interspersed with relapses.

If above is 2 or 3:
How often do you experience relapses?

1. Weekly
2. Monthly
3. Bi-monthly
4. Few times per year
5. Once a year

Would you say that, since you became ill, your symptoms are:

1. Worse than ever
2. About as bad as they have ever been
3. A bit better than they have been in the past
4. Much better than they were

When you are fatigued, do you find that resting:

1. Completely relieves you of your symptoms
2. Provides a lot of relief from symptoms
3. Relieves your symptoms to some extent
4. Doesn’t provide much relief at all
5. Doesn’t provide any relief
Have you been diagnosed with any major medical illnesses prior to or since contracting CFS?

Eg.

- Chronic hepatitis
- Hypothyroidism
- Chronic Anaemia
- Neuromuscular disorder
- Sleep Apnoea
- Narcolepsy

If Yes,

What was the condition?
When did it occur?
How were you treated?
What was the outcome?

Have you been diagnosed with/suffered from any psychiatric illnesses prior to or since contracting CFS?

Eg.

- Major depression
- An anxiety disorder

| YES | NO |

If Yes,

What was the condition?
When did it occur?
How were you treated?
What was the outcome?

Does your family have any a history of any particular medical or psychiatric illness?

| YES | NO |
If Yes, draw family tree noting diagnoses

Before you contracted CFS, did you ever experience symptoms of a physical nature that were unable to be explained medically?

Eg.

Headaches
Skin Rashes
Heart palpitations
Muscular aches etc

YES   NO

If Yes

What was their nature?

When did they occur?

How often did they occur?

Were you treated successfully for them? (If so, how?)

OR

Did they go away on their own?

Are you currently on any type of prescribed medication?

YES   NO

Details:

Do you use any kind of ‘over the counter’ medications?

YES   NO

Details:

Do you currently consume alcohol or other recreational drugs?

YES   NO
If Yes:

What?
How much?
How often?
Would you say that there was ever a time in your life that you may have had a problem with alcohol or other drugs?

YES  NO

Details:

Do you have any eye problems or conditions that you are aware of, and/or have you ever been diagnosed with an eye condition? (addresses safety of light therapy)

YES  NO

Details:

What kinds of medical examinations have you undergone for your current illness, and what were the outcomes of those examinations?

What kinds of treatments have you undergone, and what were the outcomes of those treatments?

Eg.

Anti-depressant therapy
Immunoglobulin treatment
Alternative medicine specialists
Popular CFS treatments: e.g. cold baths
Oxygen Therapy

Have you ever been a part of a support group?

YES  NO

If Yes

When?
For how long?
What was your experience of it?
Do you have a particular theory about why your illness developed and/or why it persists?

- Virus
- Immune Dysfunction
- Hormonal Problem
- Stress
- Depression etc

While we are thinking about the causes of CFS, I'd like to ask your opinion of the relative importance of psychological and biological factors to the onset and continuation of your CFS.

I'm going to give you a scale from 1 to 7, with 1 being “not at all important” and 7 being “the most important thing”, and I ask you to use this to rate the following:

1. The contribution made by emotional or psychological factors to the original development of CFS.

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2. The contribution made by emotional or psychological factors to the fact that you continue to suffer from CFS.

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3. The contribution made by biological factors to your original development of CFS.

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4. The contribution made by biological factors to the fact that you continue to suffer from CFS.

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What do you think is the most likely thing that will lead to you getting well again?

- A medical breakthrough leading to a cure
- Time and the illness running its own course
- Resting and avoiding stress
- Just pushing through
- Other

I’d like to get an idea of what your day to day life is like at the moment. To do this, I’d like you to describe your average day, starting with waking up and going through hour by hour:

Wake up time
Get up time
Breakfast
Lunch
Dinner

Major physical activities:

Major social activities:

How would you rate the attitude of your spouse/partner towards your illness?

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<th>Not at all Supportive</th>
<th>Extremely Supportive</th>
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How would you rate the attitude of your family in general towards your illness?

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<th>Not at all Supportive</th>
<th>Extremely Supportive</th>
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How would you rate the attitude of your friends towards your illness?

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<th>Extremely Supportive</th>
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Post Interview: Summarise Time-line and important factors of illness development into preliminary formulation.
APPENDIX B:

SLEEP-ACTIVITY DIARY AND INSTRUCTIONS
Daily Activity Logbook Instructions:

The aim of having you fill in this daily activity logbook for two weeks is to allow us to examine your 24-hour sleep/activity cycle.

We have made an effort to ensure that the process of keeping the logbook is as simple and least time consuming as possible so that it will neither be a burden to you nor interfere at all with your normal daily activities. Our experience suggests that filling in the log should take you around five minutes in total each day.

The most difficult part of keeping the log is remembering to fill it in. It is important that you fill it in throughout the day rather than at the end of each day, because the longer you leave the recording process, the more difficult it will be for you to accurately recall precisely what you were doing at what time and for how long. Again, our experience suggests that spending a minute filling in the log on three or four occasions throughout an average day should be enough to ensure accurate recording. If you work or move from place to place a lot, this may necessitate that you take the logbook with you for some part of the day.
Filling in the log:

You will notice that for each morning and afternoon/evening of each day throughout the two-week period, there are time-lines for each of five different types of activities: sleeping, resting, sedentary activity, heavier activity and eating. The time-lines are marked with the actual time of day, and divided into 15-minute blocks.

To fill in the log, you simply colour in or draw a clear line along the time-lines according to the times of each day you were performing each of the activities (to the nearest 15 minutes). You can use whatever texta, biro, pencil or crayon is at hand.

Definitions of Activities:

1. Sleeping

Fill in the sleeping line to represent the times that you were actually asleep. Thus, if you slept right through from 10pm until 7am, you would fill in the all the boxes of afternoon/evening timeline from 10pm until 12am, then go over the page and colour in the boxes from 12am until 7am. If, on the other hand you woke through the night (to go to the toilet or because a dog was barking etc.) you would leave the 15 minute square that corresponds to the time you woke blank, as well as any others, depending on how long you estimate that it took to get back to sleep. Obviously, doing this the next day depends on whether you looked at the clock or not when you woke up. If you didn’t, don’t worry, just make a note the next morning that you woke through the night but you don’t know when. Literally, we don’t want you to ‘lose sleep’ over filling in the log!

Did you wake naturally or use an alarm?

Above the sleeping line, you are also asked to note, by ticking the appropriate box, whether you woke up using an alarm of some kind, or if you woke naturally. If you use an alarm, but woke before it went off, tick ‘Woke naturally’.

2. Resting:

The resting line indicates time you spent either lying or sitting down and doing nothing. Fill in the resting line for those times that you weren’t sleeping, but weren’t doing anything else either.

These times would include:

- Any time you spend in bed before or after you wake up, such as the time you spend trying to get to sleep or trying to drag yourself out of bed in the morning, unless you are reading, talking, or doing anything else...(in which case you are doing something)
- Any time you spend just sitting or lying down and doing nothing else.
3. Sedentary Activity:

The Sedentary Activity line is to indicate any time you spent doing things that involved little physical activity. Most commonly, these are the kinds of activities you would perform in one spot, while you were sitting or lying down.

Examples of things that should be coded as Sedentary Activities are:

- Watching television, talking, reading, writing, studying, working at a desk or table, using a computer, etc.

4. Heavier Activity:

The Heavier Activity line is used to record the time that you spend doing things that involved higher levels of physical activity. Fill in this line when you are doing something that involves moving about. Most often, but not always, these will be things you do while you are standing up.

Examples of things that qualify as Heavier Activities are:

- Doing work around the house, walking, gardening, moving around a room (eg making dinner or getting ready to go out), and any form of exercising.

*Shady areas between Sedentary and Heavier Activity Categories:

There will be a few occasions when you will be unsure as to which of these two categories a particular activity falls into. When this happens, you need to assess how much physical activity is involved in the behaviour in question, compared to the levels of physical activity involved in the examples outlined in the Sedentary and Heavier Activity categories.

For instance:

- Sometimes you might be working at a desk most of the time, but regularly have to get up to go and do other things, such as photocopy, talk to people, get something etc... As a rule of thumb, if you are getting up three times or more in every fifteen minute period, count your activity as Heavier Activity.

5. Eating

Simply write the number 1 or 3 in the box corresponding to the time you ate to signify whether you were eating a snack or a meal. Fill in a ‘1’ if you only had a snack, or a ‘3’ if you had a meal at that time.

- A SNACK is defined as a small amount of food such as a couple of biscuits, a piece of fruit, chocolate bar, piece of bread etc..
- A **MEAL** is defined as a more substantial intake of food, that you will generally consider to be equivalent to your breakfast, lunch or dinner, even if it occurs outside those meals or the times normally associated with them.

However, if, for example, you have only a piece of fruit in the morning, but you usually think of that as breakfast, you should still code it only as a snack, because it is only a small amount of food.

**Physical and emotional wellness ratings:**

You are asked to rate how you feel physically and emotionally each morning in the hour after you wake and each night in the hour before you sleep. Use a scale from 1 to 10 to make these ratings, with ‘1’ indicating that you feel extremely unwell, and a ‘10’ indicating that you feel extremely well. If you are a healthy control participant, rate yourself compared to how you normally feel. If you are a CFS sufferer, rate yourself compared to how you felt before you became ill. A ‘10’, for instance, would mean that you felt as well as an average healthy person when they are feeling at their best.

**Example Log:**

Over the page I have provided you with an example of what a filled in log may look like at the end of a day. The log entries represent a day in the life of ‘Jane’, beginning from midday on a Saturday and ending at midday on the following Sunday.

Jane had gone out shopping late in the morning, and arrived home at about 1:40pm. After putting the shopping away and fixing herself some lunch, she settled down at about 2pm, had her lunch and spent the rest of the afternoon studying at her desk, with one ear on the radio broadcast of the Footscray-Melbourne match. By about 5:40, Footscray had been soundly beaten and she had had enough of study. She got up, had a piece of fruit and did a few things around the house before she got ready to go out to the movies with a friend.

Her friend arrived at about 6:45, and they had dinner together before taking the half hour drive (in which Jane was a passenger) into the city, followed by a 10 minute walk to the actual cinema. The movie finished at about 10pm, and they walked back to the car, and Jane’s friend dropped her off at home at around 10:45. Jane then did a few things before she settled down to watch TV for a while. Physically, she was feeling pretty tired but very content after a fun evening. At 11:30, she went off to bed, and estimates that she got to sleep at about 12:15am.

Through the night, she recalls being woken by a noise in the neighbourhood. She happened to look at the clock and it was 4:03, and she went quickly back to sleep. She woke again at 7am, but again went back to sleep almost immediately. At 8:15am she woke for the last time, but she stayed in bed for another 45 minutes relaxing and thinking about the day ahead. Because she woke without an alarm clock she ticked ‘Woke naturally’.

At 9am she got out of bed, had a quick shower and fixed herself some breakfast. Physically and emotionally, she was feeling very good. She then ate and spent about 45 minutes reading the paper and watching the Sunday morning TV. At 10am she went out to tackle some work in the garden, which kept her busy until well past midday.
### Afternoon / Evening Activity Log

**Saturday**

**Sleeping (Time you actually spent asleep)**

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<tr>
<th>Time</th>
<th>12pm</th>
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**Resting (Time you spent doing nothing apart from resting or sleeping)**

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**Sedentary Activity (Time you spent doing Things while sitting or lying down)**

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**Heavier Activity (Time you spent moving about or doing Things involving significant physical activity)**

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**Eating (When you ate: 1 = Snack, 3 = Meal)**

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Please rate from 1 to 10, how you felt *in the hour before bed-time*:

- Physically?
- Emotionally?

**Morning Activity Log**

**Sunday**

**Sleeping (Time you actually spent asleep)**

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<th>Time</th>
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Please tick: *Used Alarm to wake* ☐ *Woke naturally* ☑

**Resting (Time you spent doing nothing apart from resting or sleeping)**

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**Sedentary Activity (Time you spent doing Things while sitting or lying down)**

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**Heavier Activity (Time you spent moving about or doing Things that involved significant physical activity)**

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**Eating (When you ate: 1 = Snack, 3 = Meal)**

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Please rate from 1 to 10, how you felt *in the hour after waking*:

- Physically?
- Emotionally?
Figure A.1. Example of one participant's completed log for one 24-hour period.
APPENDIX C:

TREATMENT PROTOCOL FOR
COGNITIVE-BEHAVIOURAL
THERAPY + LIGHT
AND COGNITIVE BEHAVIOURAL THERAPY
+ PLACEBO LIGHT CONDITIONS
Chronic Fatigue Syndrome Treatment Protocol

CBT + Light (or Placebo Light) Regime.

**Assessment Phase:**

Session 1  *Meet patient (and informant if possible) in order to begin assessment process (Interview + MMPI-2).*

Session 2  *Explain treatment rationale and provide general information about CFS.*

Begin sleep-activity monitoring

Session 3  *Having received, coded and interpreted sleep-activity diary and psychometric instruments, feed back to patient. Present concept of formulation to patient and begin collaborative development of patient's illness formulation.*

**Treatment Phase**

Session 4  *Present and discuss formulation with patient as a hypothesis and basis for a treatment plan. Get patient’s commitment to treatment. Prescribe light protocol Set preliminary behavioural goals. Get patient to begin to formulate a routine.*

Session 5  *Assess progress of Light treatment. Set up goal routine & begin cognitive work.*

Session 6  *Assess progress of light sessions. Support routine implementation. Continue cognitive work.*

Session 7-9  *Review light sessions and routine. Continue cognitive work.*

Session 10  *Review, Discuss maintaining and improving upon gains. Termination.*

Total  10 Sessions over 10 weeks
Stage 1: Assessment (3 Sessions)

Prior to attending 1st interview, verification that appropriate pathological screening has been carried out has been obtained from patient's physician.

SESSION 1

Aim: Meet patient (and informant if possible) in order to begin assessment process (Interview + MMPI-2).

Brief introduction of therapist and outline of the session.

"The aim of this session is to get to know you a little and to begin a fairly comprehensive assessment of your illness.

You may already know that our approach is focused on your biological timing system with the aim of ensuring that your 24-hour biological and behavioural patterns are synchronised. I will explain this idea in more detail soon, but for now I would like to get to know more about you and your illness. The aim of this is twofold, in that firstly it is necessary to make a detailed assessment of your CFS in order for us to focus our treatment as appropriately as possible, and secondly to collect information for the purposes of the research.

You may also know that our approach is a combination of dealing with the biological and psychological aspects of the disorder. We are interested in the psychological side of things because most of the research in the area and our own experience tells us that treatment has a much better chance of success if both psychological and physiological issues are dealt with. In this respect, CFS is no different to other medical problems in that the course of many medical disorders (eg. heart disease and even cancer) may be exacerbated or influenced by psychological factors (eg stress, anxiety and a positive outlook etc.).
Does this sound reasonable to you?" (Deal briefly with any issue raised, but avoid explaining too much of the rationale at this stage, or getting into lengthy discussions with respect to aetiology).

"OK. Now what I would like to do first is to ask you a series of standard questions relating to your illness and how it came about. This will probably take about 90 minutes. After that I will explain a little more about our treatment process, and especially about the other measures we need to take in order to get a full picture of what's happening both biologically and psychologically for you at the moment. I will then get you to fill in some questionnaires and set up some things for you to do before our next session."

\textbf{Run CLINICAL INTERVIEW}

Give MMPI-2 to take home and fill out.

"This questionnaire assesses aspects of your personality. Its purpose is partly to help us to assess whether you meet the diagnostic criteria set out for the study, and partly to assess whether you have any particular worries or issues that may be important to your treatment."

Patient is asked to complete survey and post it back (envelope provided) within three days.
SESSION 2:

Aim: Explain treatment rationale and provide general information about CFS. Begin sleep-activity monitoring

Provide Handout 1: ‘Some basic facts about CFS’

Go through this handout with the patient, ensuring that the basic issues are understood.

“Our treatment program is based on our research into circadian rhythms and CFS. Go through handout 2 with patient.

Provide Handout 2: ‘The biological clock and health’

“There are a number of recent studies coming from several research centres around the world including our own which indicate that in CFS sufferers, biological rhythms may be disturbed. Although the exact origins and nature of the disturbance is not yet clear (investigating this is one of the goals of our research) an obvious conclusion that could be drawn is that this disturbance may contribute to some of the symptoms experienced in CFS.

Provide Handout 3: ‘Program Outline’

“So...our treatment program covers two major areas:

1. Dealing with any physiological (biological rhythm) disturbance, and then:
2. Working towards adapting to and dealing with the thoughts and behaviours associated with CFS.

“The program begins with the assessment of the state of your biological clock, which is achieved mainly by looking at your 24 hour rhythms of sleep and activity. Based
on the results of this assessment, we prescribe a program of bright light exposure on a
daily basis for 6 weeks. The bright light is applied at a time designed to reset and/or
strengthen the rhythm of your biological clock. In particular, the rhythm of your
clock is set so that it is synchronised with that of your sleep-wake cycle. As well as
this, we will work together to develop a routine of daily activity, which includes
sleep-wake, eating and exercise times.

“We set up a routine because research tells us that by regularising daily behavioural
patterns, the rhythm of your biological clock can be reset and/or reinforced even
without light treatments. Thus, the routine is important because it not only adds to the
synchronising effects of the light, but it will help you to remain regular after the light
treatments are finished.

The major aim of the routine is to synchronise the rhythms of your clock and sleep-
wake cycle, as it has been demonstrated that proper synchrony between these two
major rhythms is necessary for proper physiological and psychological functioning.

As well as resetting or reinforcing your biological timing system, we use an adaption
of a treatment program that has been used with some success with CFS sufferers in
the UK. The program is called cognitive-behavioural treatment because it works on
developing new ways of thinking about aspects of CFS and new behaviours or habits
that are likely to improve your ability to cope with your illness and even reduce the
number and intensity of your symptoms.

**Explanation of the assessment process:**

“At first this will entail you keeping track of your daily patterns of sleep-wake and
eating for a couple of weeks, and perhaps wearing some electronic apparatus to keep
track of your sleep-activity pattern. Following this process, which takes 2 weeks, we
will provide you with a light box and prescribe a program of light sessions for you.
It’s then up to you to follow the program at home, although we will review it here
every week. Also, we take a look at where more of a routine might be needed in your
day in terms of sleeping, eating and being active. We then work together to develop and implement a plan that’s acceptable to you. Part of each session will then be devoted to seeing how you go at implementing your plan and dealing with any difficulties that might arise.”

“The whole assessment and treatment process takes about 10 weeks.”
How does that sound to you?.. Do you have any questions?”

1. Sleep-Activity Assessment:

Explain Sleep-Activity diary, which will be filled in continuously throughout treatment

“The sleeping and eating diary helps us find out how your day is structured. Most importantly, it gives us an indication of your 24-hour pattern of sleep-wake, which we then need to compare to the timing of your biological clock in order to evaluate the presence of any desynchrony, as well as prescribe an appropriate light treatment. Another benefit of filling out the diary is that it helps you to become more aware of your daily routines, which will help us to develop a plan to enhance the light treatment.

Provide Handout 4: Sleep-activity diary & Instructions.

2. Psychometric Measures:

Provide following instruments and ask patients to fill them out and post them back with sleep activity diary on the last day of the two weeks of sleep-activity monitoring
(Provide addressed envelope with date to send written on it)

- Fatigue Assessment Inventory
- Beck Depression Inventory
- POMS
- SF-36
SESSION 3:
(Two weeks later)

Aim: Having received, coded and interpreted sleep-activity diary and psychometric instruments, feed back to patient. Present concept of formulation to patient and begin collaborative development of patient’s illness formulation.

Discuss patient’s perspective on previous sessions and what their thoughts have been since. Clear up any issues they may be unsure of. Discuss results of sleep-activity monitoring, MMPI and other measures. sleep, disturbed sleep etc.

Begin discussion of the formulation method. Explain that all the information collected so far will be synthesised to develop an explanation (educated guess) as to the reasons for the patient’s development of, and continued suffering from, CFS.

Point out that people with CFS are a heterogeneous group, and that their illness is often the result of many different factors. Communicate that the object of constructing a formulation is to tap into the particular idiosyncratic combination of factors that have contributed to the development and maintenance of the illness in the patient. This then indicates what particular treatment strategies will be appropriate for the individual. Emphasise the hypothetical nature of the formulation, and that it is likely to change over the period of intervention. Also emphasise that they have a role in the shaping of the formulation, and that a major object of the therapeutic process is to work together to hone the formulation. Discuss this, collect any further information, collaborate preliminary formulation with patient i.e: generate hypotheses.

Let patient know that you will synthesise all the information collected so far in order to present a more detailed formulation next session when, provided the formulation sits well with the patient, treatment will begin.
Stage 2: Treatment (7 Sessions)

SESSION 4:

Aim: Present and discuss formulation with patient as a hypothesis and basis for a treatment plan. Get patient's commitment to treatment. Prescribe light protocol Set preliminary behavioural goals. Get patient to begin to formulate a routine.

Formulation from assessment is presented to patient (at a level patient can understand/accept). This is done in a way that presents it as a hypothesis that is a best guess based on the available information (from the patient and from the best research into the nature of CFS).

The formulation should basically describe a theory of aetiology for the disorder that allows for the involvement of some kind of biological mechanism: eg. a virus or period of high stress impacting upon the functioning of the hypothalamic region, leading to various physical disturbances. The impact of psychological and behavioural factors on illness maintenance should then begin with the aetiological event being placed in the context of the individual's pre-morbid personality and functioning, and their reaction to their illness.

The presentation of the formulation is enhanced by simultaneous basic education of the patient regarding salient information from research into CFS. This includes:

- The effects of physical inactivity; ie. deconditioning which leads to post-exertion myalgia
- Latest research indicates that gradual increases in activity are beneficial to many sufferers
- Sleep disturbance leads to fatigue and immune disturbance
- Indication that some symptoms may be due to factors not directly CFS related, and that these can be dealt with.
These issues are dealt with only in as much as they assist the explication of the model. They will all be dealt with in more detail later during treatment.

The patient is encouraged to question the model, and it is likely that there will be a sizeable proportion of patients who are cynical about the psychological involvement in the symptom cycle. It is important to re-emphasise to them that a biological aetiology of CFS is not being undermined by the model, which merely describes a vicious cycle that serves to make the illness worse than it might otherwise be.

A description of treatment using this model may include the idea that it attempts to sort out what aspects of their symptom profile are directly related to CFS and what aspects are artefacts of the lifestyle the patient has adopted. Once these layers are ‘peeled away’ treatment can focus on the ‘really central symptoms’. This can be used to co-opt the patient into a more open-minded hypothesis testing approach to their treatment in which the therapist and patient work together to ‘explore’ the best ways to assist recovery.

If a patient remains adamant that the illness is due to purely pathological processes, the therapist might note that they could well be right, but that it may be worth trying another approach, given that there is little to lose and the success demonstrated by the purely cog-behavioural approach in the scientific literature. Of course, the fact that there is the circadian aspect to treatment, whether there is any validity to it or not, should help reduce patients’ resistance to the package as it should make it less threatening to their idea of a purely physiological basis to their illness.

The main aim of the session is to gain the patient’s commitment to the treatment program. This is obviously going to be very important to the success of any treatment undertaken. A second aim is set some behavioural goals that the patient can be working towards: eg

'Walk 3 kilometres 3 times a week by the end of treatment'.
Goals need to be negotiated realistically, keeping in mind the patient’s current level of disability.

Once these goals are set, treatment planning can begin. For the next week, the patient should continue their sleep-eating diary, and they should also be noting times when they feel the best physically through the day. These times will be looked at, and if consistent can be used as a window to introduce the exercise program.

Provide Handout 5: Development of a Daily Routine

At the same time, the patient should begin thinking more directly about the structure of their day. Indicate that building a routine entails defined bed and rising times, meal times, exercise and relaxation periods. Describe rationale for this: ie.

- Regular bed and rising times promotes healthy sleep that should prepare you better to face the challenges of the day, as well as reducing your levels of fatigue and boosting your immune system.

- Regular meal times allows your digestive system to prepare for the intake of food which leads to more efficient digestion. You thus gain greater nutritive value from your food, and the chances of gastric disturbances etc. are greatly reduced.

- Regular exercise times also mean your body is more prepared to work and gain greater benefits from the activity. The negative effects of exercise are reduced by its regular performance at a time of day that you feel most able to cope with it.

- For the same reasons, regular relaxation times will make it easier to relax. We suggest these are set up for a few hours before bed time to assist your body in the wind-down process.
Note that the main aim of all of this regularity is to provide an externally imposed structure on the internal timing system to assist the overall efficiency of biological, behavioural and psychological functioning. Start this process by developing a basic sleep-wake schedule with the patient. If this varies significantly from their current one, develop a series of graded steps towards goal schedule.

*Provide Handout 6: Light Box Prescription.*

Patient is provided with a written program for light exposure that fits within their routine. For the Bright Light group, the maintenance dose is between 2,500 and 5,000 lux for around 45 minutes per day. If rhythms need to be adjusted significantly i.e., phasic advanced, then longer exposures can be used at first, until the desired sleep-wake schedule is achieved. It is explained to them how to use the box. This should focus on the importance of maintaining a particular distance from the box in order to get the proper dose, as well as the amount of time necessary. CBT+Placebo group get subtherapeutic red light, so adjustments in phase will need to be slower.

Provide simplified sleep log that will be used to monitor sleep patterns through treatment (Example included in Appendix F).

**Homework:**

- Begin light exposure
- Completion of the sleep log, as well as setting up a temporal framework for the patients day

This should entail goals with respect to:

1. Bed-time
2. Rising-time
3. Breakfast, Lunch, Dinner & any snack times if necessary.
4. Exercise period
5. Relaxation period
The patient may need to be reassured that it is not expected that they will necessarily be able to hold to these times precisely and right away, but rather that they provide a basic routine that will be aimed for and, hopefully, achieved, over the whole course of treatment. The patient can begin to try to implement a routine if they wish, although they should be encouraged to proceed cautiously. They may be able to reality test a couple of plans before the next session, and if they have tried to perform their routine by the next session, it will provide more concrete material to talk about.

It may also be worth discussing that to give the treatment a real chance, the patient really needs to set their recovery as the highest priority for the time being.
SESSION 5:

Aim: *Assess progress of Light treatment. Set up goal routine & begin cognitive work.*

Review the light program and sleep log. Deal with any issues; eg. ‘light uncomfortable to look at’ (sit further away but for longer). Discuss subjective effects, provide encouragement if patient has experienced no changes.

Review patient’s homework; ie. sleep log and goal routine outline. Compare what the present routine (or non-routine) is like with the goal routine. Is it very different... too different to be realistic or not different enough? Negotiating an appropriate regime from here needs to balance the aims and realistic capabilities (current disability) of the patient with the actual factors necessary for medical and psychological recovery.

*For instance:*

**Sleep.**

Different people need different amounts. A good indicator of how much sleep the patient should aim for might be how much they had when they were healthy (well before illness onset). So, if someone slept for 7 hours on average when they were well, that should be the present target. Patients may feel they need more now, and this may be true, especially if the sleep they do have is disturbed.

Thus, the time between bed and rising times should approximate the amount of time slept per night pre-morbidly, with perhaps some extra time (say half to one hour at most) to allow for poor quality sleep. The bed itself should be a restricted zone, only accessible at these agreed upon hours.
When a patient is sleeping excessively beyond premorbid functioning, it may be impossible to immediately restrict bed times, and in this case a gradual reduction should be aimed at. Provide patient with an information sheet on things they can do to aid their sleep eg reduce or eliminate caffeine, alcohol, cigarettes etc. Sleep hygiene (clean environment free of noise and light and interruptions)

**Provide Handout 7: Some Tips for Healthy sleep.**

Go through and explain each of the tips on the handout.

**Eating**

The research indicates that the human digestive system entrains best to three evenly spaced meals per day. To spread these through the day, 4-5 hour approximate separations make reasonable sense. eg. 9am, 1pm and 6pm. These should be set out as eating windows through the day, with perhaps an hour in which to commence a meal (eg. breakfast should start between 8:30 and 9:30).

Aspects of the patient’s social environment will need to be considered, eg, when a partner normally returns from work etc.

**Exercising**

The literature indicates that exercise (actually the increase in body temperature related to it) about 6 hours before sleep onset is the most beneficial in terms of healthy sleep promotion. However, the benefits of exercise are not just in its sleep promoting effects, and the CFS patient may not be at their physical best at that particular time of day. At this stage, use the information as to the window of the day when the person themselves feels that they are normally most able to deal with physical activity to determine the exercise time.
The nature of the exercise itself will depend entirely on the capacity of the individual, and it is very important at this stage to ensure that they do not overdo their 'work-out'. Start exercise well within the limits of the individual, and set a course of gradual increases in intensity aimed at achieving the realistic goals set for the end of treatment. Walking is the main form of exercise suggested.

Relaxing

Relaxing should be set up as an active pursuit rather than just 'voging'. Use of progressive muscle relaxation may be appropriate, or perhaps a relaxation tape. Breathing exercises may be introduced, especially if chest rather than diaphragmatic breathing is a characteristic of the patient. In such cases, 5 or 10 minute breathing exercises can be implemented morning, noon and night as both a breathing retraining schedule and to assist at lowering baseline arousal (anxiety).

The main relaxation exercise should be performed at night, preferably as a part of the patient's 'wind down' ritual towards bed-time. If patient is unsure about meditation etc, a hot bath may be just as good, and serves to increase core temp prior to bed-time. This may help to induce sleep as the body attempts to cool down, and may lead to a lower night-time temperature trough.

'Day is for activity, night is for rest'

The overall model the patient should be presented with is regularity with the aim of making day and night as different as possible. From waking, the focus should be on activity designed to arouse the individual, both in a physical and mental sense. This should peak with the exercise period (depending on its timing). After the evening meal, the emphasis should change to a winding down towards the sleep period. Apart from their relaxation etc., patients should avoid bright light and other arousing stimuli, such as caffeine or physically or emotionally stressful activities. Nonetheless, the patient should try to engage in some sort of activity, such as reading, socialising etc.
Commence Cognitive Component

By this stage, the patient has a lot of changes to implement, and it needs to be judged whether or not they might be able to begin the cognitive work at the same time, or whether it is best to leave it until next week when they have tried implementation and the investigation on a cognitive level of the obstacles may be more obviously salient. On the other hand, because the patient will be implementing changes in the next week, it is likely to be a good time to commence monitoring of negative thoughts. This will form the beginning of the process of helping patients become aware of their habitual ways thinking and acting in response to symptoms (specifically) and their illness (generally). Following this they will be assisted in re-evaluating these responses (adaptive vs maladaptive) and implementing different responses (adaptive) where necessary.

Discuss with the patient the likelihood of obstacles becoming apparent in the next week or so. Normalise this response, and convey to the patient that it represents an opportunity to investigate the way they feel about their symptoms and their illness, and whether there might be ways of making their transition easier.

Provide Handout 8: Monitoring & Challenging Negative Thoughts.

Show them the ‘Double column technique’. In this, the self monitor their negative thoughts at times of frustration etc. and write them down in the first column (Original thought). They then are challenged to come up with a more positive/adaptive alternative to the thought in the second column. It may be enough this week to have them only monitor their thoughts (e.g. I’ll never get better, it’s too hard...) and the process of challenging them can be demonstrated next session.

Homework:
- Continue Light
- Begin to implement routine
- Continue sleep log.
- Monitor negative thoughts in relation to the treatment and the illness.
SESSION 6:


Review the light program and sleep diary. Deal with any issues. Fatigue and other symptoms may be increasing at first because of the new measures being taken. Assure patient that this is to be expected and reinforce that they aren’t doing any pathological damage, and that things should become easier.

Go through homework, compare routine plan with what has actually happened. Provide support for the patient who is likely to be experiencing some difficulties implementing the routine. Negotiate to adjust the routine where necessary.

Go through thoughts. Assist in challenging unrealistic illness attributions and pessimistic views of treatment chances. Demonstrate the procedure for generating positive (realistic) alternatives.

Return to formulation and reinforce or adjust where necessary.

Homework:
- Continue filling out Sleep-log
- Negative thoughts and alternative thoughts diary
SELECTIONS 7-9

Aim: Review light sessions and routine. Continue cognitive work.

Review light sessions and sleep-log. Compare activity patterns with routine plan. Discuss issues/obstacles. Some adjustments may have to be made. Mood may have gone either way: down, because of hassles confronted and fears that treatment isn’t going to work, or up, because of increase in sense of control or self-efficacy.

At this stage, if patient is experiencing improvements, it may be important to begin preparing patient to adopt a ‘well’ role, and the changes in responsibilities that go with it. Obstacles to returning to some form of work or domestic responsibility will need to be assessed and discussed. It may also be appropriate to deal with ingrained attitudes, such as perfectionism. Given that, if present, they may be entrenched, it is likely that, the goal of the therapy may be only to help the patient realise that they are there and, perhaps, how they interact with cognitions to worsen patients reactions to let-downs etc.

Review the negative thoughts and positive alternatives. Again, discussions should keep the formulation in mind, and this should be being modified and honed in line with the atmosphere of open investigation of the illness and ways of dealing with it. It is also important to begin to help the patient notice that they may have been misattributing some of their symptoms to CFS, when they were actually artefacts of their lifestyle or other psych or medical problem. This is important because it helps them to see that although they may think CFS is incurable, many of the symptoms they have can be dealt with.

Sleep, mood, anxiety problems should be dealt with where necessary. Implement education and problem solving to assist patient with any particular problems they may have. Begin preparation for termination of therapy.
SESSION 10

Aim: Review, Discuss maintaining and improving upon gains, Termination.

Treatment concludes, patient returns light box. Conduct final review of the sleep logs and program. Look at ratings from the sleep-log, and compare with ratings from pre-treatment. If no effect, patient may be frustrated or depressed. This will need to be dealt with sensitively. Suggestions for further action may be made. If there are gains, discuss them and what they might mean for tackling further problems. Patient may be encouraged to seek light in the mornings (natural light) or even buy a light-box for their own use (if they found it beneficial).

In the final session, Sharpe (1996) suggests that the patient should produce a written document that includes the final formulation and the things learned from therapy. This document can also be used to list ways in which the patient can continue with rehabilitation and deal with relapses. This should be done with a view to the patient continuing their own treatment from here on and dealing with relapses should they occur.

Thank patient for their involvement, provide sleep-activity log and outcome measures to be filled out over the next two weeks. Remind them about the 6-month follow-up and indicate when overall results will be available.
APPENDIX D:

TREATMENT PROTOCOL FOR LIGHT AND PLACEBO LIGHT CONDITIONS
Chronic Fatigue Syndrome Treatment Protocol
Light (or Placebo Light) Regime.

**Assessment Phase:**

**Session 1**  
*Meet patient (and informant if possible) in order to begin assessment process (Interview + MMPI-2).*

**Session 2**  
*Explain treatment rationale and provide general information about CFS. Begin sleep-activity monitoring.*

**Session 3**  
*Having received, coded and interpreted sleep-activity diary and psychometric instruments, feed back to patient.*

**Treatment Phase**

**Session 4**  
*Present and discuss treatment plan. Get patient’s commitment to treatment. Prescribe light protocol.*

**Session 5**  
*Assess progress of Light treatment, adjust if necessary.*

**Session 6 & 7**  
*Assess progress of Light treatment, adjust if necessary.*

**Session 8**  
*Review, Discuss maintaining and improving upon gains, Termination.*

**Total**  
8 Sessions over 10 weeks
Stage 1: Assessment (3 Sessions)

Prior to attending 1st interview, verification that appropriate pathological screening has been carried out has been obtained from patient’s physician.

SESSION 1

Aim: Meet patient (and informant if possible) in order to begin assessment process (Interview + MMPI-2).

Brief introduction of therapist and outline of the session.

“The aim of this session is to get to know you a little and to begin a fairly comprehensive assessment of your illness.

You may already know that our approach is focused on your biological timing system with the aim of ensuring that your 24-hour biological and behavioural patterns are synchronised. I will explain this idea in more detail soon, but for now I would like to get to know more about you and your illness. The aim of this is twofold, in that firstly it is necessary to make a detailed assessment of your CFS in order for us to focus our treatment as appropriately as possible, and secondly to collect information for the purposes of the research. Does this sound reasonable to you?” (Deal briefly with any issue raised, but avoid explaining too much of the rationale at this stage).

“OK. Now what I would like to do first is to ask you a series of standard questions relating to your illness and how it came about. This will probably take about 90 minutes. After that I will explain a little more about our treatment process, and especially about the other measures we need to take in order fulfil both the research and treatment goals of the project. I will then get you to fill in some questionnaires and set up some things for you to do before our next session.
Run CLINICAL INTERVIEW

Give MMPI-2 to take home and fill out.

"This questionnaire assesses aspects of your personality. Its purpose is mainly to help us to assess whether you meet the diagnostic criteria set out for the study.

Patient is asked to complete survey and post it back (envelope provided) within three days.

SESSION 2:

Aim: Explain treatment rationale and provide general information about CFS. Begin sleep-activity monitoring

Provide Handout 1: ‘Some basic facts about CFS’

Go through this handout with the patient, ensuring that the basic issues are understood.

"Our treatment program is based on our research into circadian rhythms and CFS. Go through handout 2 with patient.

Provide Handout 2: ‘The biological clock and health’

"There are a number of recent studies coming from several research centres around the world including our own which indicate that in CFS sufferers, biological rhythms may be disturbed. Although the exact origins and nature of the disturbance is not yet clear (investigating this is one of the goals of our research) an obvious conclusion that
could be drawn is that this disturbance may contribute to some of the symptoms experienced in CFS.

Provide Handout 3: ‘Program Outline’

"The program begins with the assessment of the state of your biological clock, which is achieved mainly by looking at your 24 hour rhythms of sleep and activity. Based on the results of this assessment, we prescribe a program of bright light exposure on a daily basis for 6 weeks. The bright light is applied at a time designed to reset and/or strengthen the rhythm of your biological clock. In particular, the rhythm of your clock is set so that it is synchronised with that of your sleep-wake cycle.

"We will also ask you to maintain a relatively regular sleep-wake pattern throughout the treatment period. The reason for this is in order to synchronise the rhythms of your clock and sleep-wake cycle, as it has been demonstrated that proper synchrony between these two major rhythms is necessary for proper physiological and psychological functioning.

Explanation of the assessment process:

"At first this will entail you keeping track of your daily patterns of sleep-wake and eating for a couple of weeks, and perhaps wearing some electronic apparatus to keep track of your sleep-activity pattern. Following this process, which takes 2 weeks, we will provide you with a light box and prescribe a program of light sessions for you. It’s then up to you to follow the program at home, although we will have sessions here to review it on a regular basis. These sessions are aimed at seeing how the treatment is proceeding and dealing with any difficulties that might arise.

"The whole assessment and treatment process takes about 10 weeks."
How does that sound to you? Do you have any questions?"
1. **Sleep-Activity Assessment:**

Explain Sleep-Activity diary, which will be filled in continuously throughout treatment.

"The sleeping and eating diary helps us find out how your day is structured. Most importantly, it gives us an indication of your 24-hour pattern of sleep-wake, which we then need to compare to the timing of your biological clock in order to evaluate the presence of any desynchrony, as well as prescribe an appropriate light treatment.

*Provide Handout 4: Sleep-activity diary & Instructions.*

2. **Psychometric Measures:**

Provide following instruments and ask patients to fill them out and post them back with sleep activity diary on the last day of the two weeks of sleep-activity monitoring (Provide addressed envelope with date to send written on it)

- Fatigue Assessment Inventory
- Beck Depression Inventory
- POMS
- SF-36
SESSION 3:
(Two weeks later)

Aim: Having received, coded and interpreted sleep-activity diary and psychometric instruments, feedback to patient.

Discuss patient’s perspective on previous sessions and what their thoughts have been since. Clear up any issues they may be unsure of. Discuss results of sleep-activity monitoring, MMPI and other measures. sleep, disturbed sleep etc.

Let patient know that you will synthesise all the information collected so far in order to present a more detailed profile and treatment plan at the next session.
Stage 2: Treatment (7 Sessions)

SESSION 4:

Prescribe light protocol.

Go through results of sleep-activity monitoring, focussing on sleep times, wake times, disturbed sleep etc. Discuss rationale for the use of the light “to set and regularise the timing of your biological clock so that it synchronises with your pattern of sleep-wake”. Explain that this “also requires that you maintain a fairly regular schedule of sleep and wake times”. Discuss appropriate sleep-wake schedule and the appropriate timing of the light within this. Generally the aim will be to schedule light exposure to occur within a half-hour of waking. For the Bright Light group, the maintenance dose is between 2,500 and 5,000 lux for around 45 minutes per day. If rhythms need to be adjusted significantly (Light group only) ie, phase advanced, then longer exposures can be used at first, until the desired sleep-wake schedule is achieved. For the Placebo light group, non-therapeutic red light is used. Suggest that they focus on regularity for the period of the study, rather than make any large changes in their sleep-wake pattern.

Provide Handout 6: Light Box Prescription.

Patient is provided with a written program for light exposure that fits within their routine. It is explained to them how to use the box. This should focus on the importance of maintaining a particular distance from the box in order to get the proper dose, as well as the amount of time necessary. Provide simplified sleep log that will be used to monitor sleep patterns through treatment (example included in Appendix F).

Homework:
- Begin light exposure
- Completion of the sleep log.
SESSION 5:
(One week later)

Aim: Assess progress of Light treatment, adjust if necessary.

Review the light program and sleep log. Deal with any issues; eg. ‘light uncomfortable to look at’ (sit further away but for longer). Discuss subjective effects, provide encouragement if patient has experienced no changes.

Review patient’s homework; ie. sleep log and discuss any issues that arise from this.

Homework:
• Continue Light
• Continue sleep log.

SESSIONS 6 & 7:
(Two-week intervals)

Aim: Assess progress of Light treatment, adjust if necessary.

Review the light program and sleep log. Deal with any issues; eg. ‘light uncomfortable to look at’ (sit further away but for longer). Discuss subjective effects, provide encouragement if patient has experienced no changes.

Review patient’s homework; ie. sleep log and discuss any issues that arise from this.

Homework:
• Continue Light
• Continue sleep log.
SESSION 8:

One week after Session 7

Aim: Review, Discuss maintaining and improving upon gains, Termination.

Finish light treatment, patient returns light box. Review sleep logs and program. Look at ratings from the sleep-log, and compare with ratings from pre-treatment. If no effect, patient may be frustrated or depressed. This will need to be dealt with sensitively. Suggestions for further action may be made. If there are gains, discuss them and what they might mean for tackling further problems. Patient may be encouraged to seek light in the mornings (natural light) or even buy a light-box for their own use (if they found it beneficial).

Thank patient for their involvement, provide sleep-activity log and outcome measures to be filled out over the next two weeks. Remind them about the 6-month follow-up and indicate when overall results will be available.
APPENDIX E:

TREATMENT PROTOCOL HANDOUTS
Handout 1: Some Basic Facts about Chronic Fatigue Syndrome.


The cause of CFS is unknown.

Although there have been many studies that have sought to explain the occurrence of CFS in terms of a single cause (ie. a virus, psychological illness, stress etc), none have been successful. Many CFS sufferers appear to have a viral illness before their CFS begins, but a large proportion of sufferers don’t.

At the moment, the best scientific opinion is that the disorder is likely to be the result of a number of factors acting together to produce the illness. These might include; a number of different viruses, stress, lifestyle and the biological and psychological susceptibility of the individual at the time of illness onset.

It is thought that it is likely that these factors act somehow to disturb an area of a sufferers brain (the hypothalamus) that regulates many of our day to day functions such as hormonal patterns, temperature regulation, sleep-wake and hunger. This is currently the major focus of much of the research around the world, including our own.

There is no diagnostic test for CFS.

Although CFS sufferers have been found to have a number of physiological differences to healthy people, these differences are either not consistent enough (ie. not every CFS sufferer displays them) or not specific enough (ie. the abnormality occurs in many medical conditions) to clearly differentiate CFS sufferers from people with other illnesses.

How common is CFS?

Recent studies of the occurrence of CFS in the general community suggests a rate of about 2 cases per 1000 people.
There is currently no established cure for CFS

Generally, sufferers find that their symptoms improve over time however, the illness can take several years to resolve completely. Although some medical interventions can help with some symptoms of CFS, at this stage, there is no medical treatment that has been scientifically demonstrated to significantly improve the condition.

You can improve your health and speed your recovery

Despite the fact that a cure is not currently available, there are things you can do to improve your health. The most success of any treatment assessed scientifically has been achieved by a type of treatment called cognitive-behaviour therapy (CBT). This treatment focuses on helping sufferers deal with their illness in ways that promote good health and are likely to enhance the natural healing processes of the body. Recent developments in the area of CBT for CFS sufferers has shown that more than 80% of CFS sufferers gain significant relief from their illness, and a significant proportion improve dramatically. CBT plays an important part in our own treatment program.

Exercise and CFS

The jury is still out on exercise and CFS. It would seem that for many, and perhaps most sufferers, a program of VERY GRADUAL increases in regular exercise can have very positive results. It can't be overstated however, that any exercise program needs to be done in consultation with a health professional familiar with CFS, and it must be carefully controlled. Overdoing exercise can result in a major relapse. There does appear to be a group of CFS sufferers for whom even small amounts of exercise are inappropriate, at least for a while. This further emphasises the importance of conducting exercise in consultation with your medical or rehabilitation therapist.
Handout 2: The Biological Clock and Health.

What are circadian rhythms?

The term ‘circadian rhythm’ refers to any cycle that is repeated every 24 hours. Circadian rhythms are apparent in many aspects of our physical and behavioural functioning. For instance, our sleep-wake cycle is an example of a circadian rhythm because it has a regular 24-hour pattern. Our body temperature also displays a circadian rhythm, in that it cycles between warmer day-time levels (e.g., around 37.5 Celsius) and cooler night temperatures (around 36.5 Celsius). See figure 1.

![Physical Activity vs. Time of Day](image1.png)

![Core Temperature Level vs. Time of Day](image2.png)

Figure 1. 24-hour patterns of physical activity (top) and core body temperature (bottom) of a 30-year-old man averaged over 3 days.

There are many aspects of our biological and behavioural functions that display pronounced 24-hour rhythms. Examples of other biological rhythms are found in
hormone levels (e.g., melatonin, cortisol & growth hormone), the activity of our immune systems (e.g., natural-killer cells) and even our blood pressure. In fact, there are well over 100 different circadian rhythms that have been found to occur in the human body.

**The ‘Biological Clock’**

As you might imagine, all of these different rhythms or cycles need to be coordinated in order for the body to function properly. The mechanism that co-ordinates or synchronises the various rhythms is called the ‘biological clock’. It occupies a small area near the middle of the brain and is part of an organ called the hypothalamus. The biological clock sets itself to the time of day by sensing the light-dark cycle of the environment and the social habits of the individual. It then sends this information to the various systems throughout the body so they become synchronised. In this way, the biological clock acts like the conductor of an orchestra, keeping everything in time so that the result is music rather than noise.

**What happens when the biological clock isn’t right?**

The most well known health problem associated with the biological clock is jet-lag, which occurs while the biological clock resets itself to a new time-zone. Jet-lag is associated with tiredness, headaches, digestive and concentration problems. The negative health effects of shift work are also related to the constant undermining of the biological clock.

More recently, scientists have investigated more subtle health effects of disturbances to the biological clock. For instance, there is evidence that irregular eating patterns can: 1. reduce the efficiency of our digestive system at obtaining nutrients from food, 2. make it more likely that calories will be stored as fat, and 3. increase our vulnerability to gastric disturbances such as indigestion and ulcers.

Another important area of investigation has been into what occurs when there is a desynchrony between the biological clock and a person’s sleep-wake patterns. When these two rhythms are out of synchrony, some fairly clear symptoms result, such as poor or non-restful sleep, immune disturbances and depressed mood. These symptoms can be cured by a resynchronisation of the biological clock and sleep-wake, using a combination of bright light exposure and a regular sleep-activity pattern.

**How could this relate to CFS?**

Many of the symptoms associated with a disturbance to the biological clock (fatigue, sleep, immune and mood disturbances) are found in people who suffer from CFS. Also, our own research and that of several other international groups have demonstrated that the circadian systems of CFS sufferers may be compromised in a number of ways. It is therefore possible that a disturbance to the biological clock may play some part in the onset and course of CFS.
Handout 3: Program Outline
(CBT+Light & CBT+Placebo Light Groups)

Assessment Phase:

First you will be interviewed and asked to answer a number of questionnaires about your symptoms, mood and level of incapacity. Then we will ask you to keep track of your 24-hour patterns of activity (Sleep-wake, eating, exercise and symptoms). Apart from providing information about the way your day to day life is structured, this information is important in establishing whether your biological clock is functioning appropriately.

Treatment Phase:

Following the assessment process, we combine the information so that we can get a good picture of what is going on for you physically, behaviourally and psychologically. This helps us establish what factors are likely to be important in the development and maintenance of your illness, which, in turn, provides us with targets for your treatment program.

The treatment program has several aspects

1. Light

You will be given a program of bright light exposure on a daily basis for six weeks. When it is delivered at the right time, light can reset the clock. So, we prescribe the light at a time that is designed to reset your clock to the right time, and keep it stable.

2. Daily Routine

We will also try to help you get into a daily routine of regular sleeping, eating and activity patterns, because this will enhance the effects of the light, and help your clock stay on time when the light treatment is finished. Regular routines by themselves are enough to reset and maintain the clock.

3. Cognitive-Behavioural Work

Throughout the treatment process, we will use some methods that are called cognitive-behavioural techniques. These techniques have been scientifically evaluated in their application with sufferers of CFS, and have been found to be beneficial. The main focus of this part of the treatment is on providing you with information about CFS, re-evaluating some of your patterns of thinking and acting in relation to your illness and replacing them with other ways that may help you to better deal with your symptoms and improve your rate of recovery.
Handout 3: Program Outline
(Light & Placebo Light Groups)

Assessment Phase:

First you will be interviewed and asked to answer a number of questionnaires about your symptoms, mood and level of incapacity. Then we will ask you to keep track of your 24-hour patterns of activity (Sleep-wake, eating, exercise and symptoms). Apart from providing information about the way your day-to-day life is structured, this information is important in establishing whether your biological clock is functioning appropriately.

Treatment Phase:

Based on the information we obtain about your sleep cycle, we will prescribe a program of bright light exposure on a daily basis for six weeks. When it is of the right type and brightness, of long enough duration and given at the right time, light can reset the clock. So, we prescribe the light at a time that is designed to reset your clock to the right time, and keep it stable.

We will loan you a light box made especially for this kind of treatment for the 6 week period so that you can follow the treatment program at home. We will make several appointments with you during that time to check how the program is going and to adjust it where necessary.
Handout 4:

Daily Activity Logbook Instructions:

The aim of having you fill in this daily activity logbook for two weeks is to allow us to examine your 24-hour sleep/activity cycle.

We have made an effort to ensure that the process of keeping the logbook is as simple and least time consuming as possible so that it will neither be a burden to you nor interfere at all with your normal daily activities. Our experience suggests that filling in the log should take you around five minutes in total each day.

The most difficult part of keeping the log is remembering to fill it in. It is important that you fill it in throughout the day rather than at the end of each day, because the longer you leave the recording process, the more difficult it will be for you to accurately recall precisely what you were doing at what time and for how long. Again, our experience suggests that spending a minute filling in the log on three or four occasions throughout an average day should be enough to ensure accurate recording. If you work or move from place to place a lot, this may necessitate that you take the logbook with you for some part of the day.
Filling in the log:

You will notice that for each morning and afternoon/evening of each day throughout the two week period, there are time-lines for each of five different types of activities; sleeping, resting, sedentary activity, heavier activity and eating. The time-lines are marked with the actual time of day, and divided into 15 minute blocks.

To fill in the log, you simply colour in or draw a clear line along the time-lines according to the times of each day you were performing each of the activities (to the nearest 15 minutes). You can use whatever texta, biro, pencil or crayon is at hand.

Definitions of Activities:

1. **Sleeping**

Fill in the sleeping line to represent the times that you were actually asleep. Thus, if you slept right through from 10pm until 7am, you would fill in the all the boxes of afternoon/evening time-line from 10pm until 12am, then go over the page and colour in the boxes from 12am until 7am. If, on the other hand you woke through the night (to go to the toilet or because a dog was barking etc.) you would leave the 15 minute square that corresponds to the time you woke blank, as well as any others, depending on how long you estimate that it took to get back to sleep. Obviously, doing this the next day depends on whether you looked at the clock or not when you woke up. If you didn’t, don’t worry, just make a note the next morning that you woke through the night but you don’t know when. Literally, we don’t want you to ‘lose sleep’ over filling in the log!

**Did you wake naturally or use an alarm?**

Above the sleeping line, you are also asked to note, by ticking the appropriate box, whether you woke up using an alarm of some kind, or if you woke naturally. If you use an alarm, but woke before it went off, tick ‘Woke naturally’.

2. **Resting:**

The resting line indicates time you spent either lying or sitting down and doing nothing. Fill in the resting line for those times that you weren’t sleeping, but weren’t doing anything else either.

These times would include:

- Any time you spend in bed before or after you wake up, such as the time you spend trying to get to sleep or trying to drag yourself out of bed in the morning, unless you are reading, talking, or doing anything else...(in which case you are doing something)
- Any time you spend just sitting or lying down and doing nothing else.
3. Sedentary Activity:

The Sedentary Activity line is to indicate any time you spent doing things that involved little physical activity. Most commonly, these are the kinds of activities you would perform in one spot, while you were sitting or lying down.

Examples of things that should be coded as Sedentary Activities are:

- Watching television, talking, reading, writing, studying, working at a desk or table, using a computer, etc.

4. Heavier Activity:

The Heavier Activity line is used to record the time that you spend doing things that involved higher levels of physical activity. Fill in this line when you are doing something that involves moving about. Most often, but not always, these will be things you do while you are standing up.

Examples of things that qualify as Heavier Activities are:

- Doing work around the house, walking, gardening, moving around a room (eg making dinner or getting ready to go out), and any form of exercising,

*Shady areas between Sedentary and Heavier Activity Categories:

There will be a few occasions when you will be unsure as to which of these two categories a particular activity falls into. When this happens, you need to assess how much physical activity is involved in the behaviour in question, compared to the levels of physical activity involved in the examples outlined in the Sedentary and Heavier Activity categories.

For instance:

- Sometimes you might be working at a desk most of the time, but regularly have to get up to go and do other things, such as photocopy, talk to people, get something etc. As a rule of thumb, if you are getting up three times or more in every fifteen-minute period, count your activity as Heavier Activity.

5. Eating

Simply write the number 1 or 3 in the box corresponding to the time you ate to signify whether you were eating a snack or a meal. Fill in a ‘1’ if you only had a snack, or a ‘3’ if you had a meal at that time.

- A **SNACK** is defined as a small amount of food such as a couple of biscuits, a piece of fruit, chocolate bar, piece of bread etc.
- A **MEAL** is defined as a more substantial intake of food, that you will generally consider to be equivalent to your breakfast, lunch or dinner, even if it occurs outside those meals or the times normally associated with them.

However, if, for example, you have only a piece of fruit in the morning, but you usually think of that as breakfast, you should still code it only as a snack, because it is only a small amount of food.

**Physical and emotional wellness ratings:**

You are asked to rate how you feel physically and emotionally each morning in the hour after you wake and each night in the hour before you sleep. Use a scale from 1 to 10 to make these ratings, with '1' indicating that you feel extremely unwell, and a '10' indicating that you feel extremely well. If you are a healthy control participant, rate yourself compared to how you normally feel. If you are a CFS sufferer, rate yourself compared to how you felt before you became ill. A '10', for instance, would mean that you felt as well as an average healthy person when they are feeling at their best.

**Example Log:**

Over the page I have provided you with an example of what a filled in log may look like at the end of a day. The log entries represent a day in the life of 'Jane', beginning from midday on a Saturday and ending at midday on the following Sunday.

Jane had gone out shopping late in the morning, and arrived home at about 1:40pm. After putting the shopping away and fixing herself some lunch, she settled down at about 2pm, had her lunch and spent the rest of the afternoon studying at her desk, with one ear on the radio broadcast of the Footscray-Melbourne match. By about 5:40, Footscray had been soundly beaten and she had had enough of study. She got up, had a piece of fruit and did a few things around the house before she got ready to go out to the movies with a friend.

Her friend arrived at about 6:45, and they had dinner together before taking the half hour drive (in which Jane was a passenger) into the city, followed by a 10 minute walk to the actual cinema. The movie finished at about 10pm, and they walked back to the car, and Jane's friend dropped her off at home at around 10:45. Jane then did a few things before she settled down to watch TV for a while. Physically, she was feeling pretty tired but very content after a fun evening. At 11:30, she went off to bed, and estimates that she got to sleep at about 12:15am.

Through the night, she recalls being woken by a noise in the neighbourhood. She happened to look at the clock and it was 4:03, and she went quickly back to sleep. She woke again at 7am, but again went back to sleep almost immediately. At 8:15am she woke for the last time, but she stayed in bed for another 45 minutes relaxing and thinking about the day ahead. Because she woke without an alarm clock she ticked 'Woke naturally'.

At 9am she got out of bed, had a quick shower and fixed herself some breakfast. Physically and emotionally, she was feeling very good. She then ate and spent about 45 minutes reading the paper and watching the Sunday morning TV. At 10am she went out to tackle some work in the garden, which kept her busy until well past midday.
AFTERNOON / EVENING ACTIVITY LOG

SLEEPING (Time you actually spent asleep)

<table>
<thead>
<tr>
<th>12pm</th>
<th>1pm</th>
<th>2pm</th>
<th>3pm</th>
<th>4pm</th>
<th>5pm</th>
<th>6pm</th>
<th>7pm</th>
<th>8pm</th>
<th>9pm</th>
<th>10pm</th>
<th>11pm</th>
</tr>
</thead>
</table>

RESTING (Time you spent doing nothing apart from resting or sleeping)

<table>
<thead>
<tr>
<th>12pm</th>
<th>1pm</th>
<th>2pm</th>
<th>3pm</th>
<th>4pm</th>
<th>5pm</th>
<th>6pm</th>
<th>7pm</th>
<th>8pm</th>
<th>9pm</th>
<th>10pm</th>
<th>11pm</th>
</tr>
</thead>
</table>

SEDENTARY ACTIVITY (Time you spent DOING THINGS while sitting or lying down)

<table>
<thead>
<tr>
<th>12pm</th>
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<th>11pm</th>
</tr>
</thead>
</table>

HEAVIER ACTIVITY (Time you spent moving about or DOING THINGS involving significant physical activity)

<table>
<thead>
<tr>
<th>12pm</th>
<th>1pm</th>
<th>2pm</th>
<th>3pm</th>
<th>4pm</th>
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<th>9pm</th>
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<th>11pm</th>
</tr>
</thead>
</table>

EATING (When you ate: 1 = Snack, 3 = Meal)

<table>
<thead>
<tr>
<th>12pm</th>
<th>1pm</th>
<th>2pm</th>
<th>3pm</th>
<th>4pm</th>
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</tr>
</thead>
</table>


MORNING ACTIVITY LOG

SLEEPING (Time you actually spent asleep) Please tick: Used Alarm to wake [ ] Woke naturally [ ]

<table>
<thead>
<tr>
<th>12am</th>
<th>1am</th>
<th>2am</th>
<th>3am</th>
<th>4am</th>
<th>5am</th>
<th>6am</th>
<th>7am</th>
<th>8am</th>
<th>9am</th>
<th>10am</th>
<th>11am</th>
</tr>
</thead>
</table>

RESTING (Time you spent doing nothing apart from resting or sleeping)

<table>
<thead>
<tr>
<th>12am</th>
<th>1am</th>
<th>2am</th>
<th>3am</th>
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<th>11am</th>
</tr>
</thead>
</table>

SEDENTARY ACTIVITY (Time you spent DOING THINGS while sitting or lying down)

<table>
<thead>
<tr>
<th>12am</th>
<th>1am</th>
<th>2am</th>
<th>3am</th>
<th>4am</th>
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<th>9am</th>
<th>10am</th>
<th>11am</th>
</tr>
</thead>
</table>

HEAVIER ACTIVITY (Time you spent moving about or DOING THINGS that involved significant physical activity)

<table>
<thead>
<tr>
<th>12am</th>
<th>1am</th>
<th>2am</th>
<th>3am</th>
<th>4am</th>
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<th>11am</th>
</tr>
</thead>
</table>

EATING (When you ate: 1 = Snack, 3 = Meal)

<table>
<thead>
<tr>
<th>12am</th>
<th>1am</th>
<th>2am</th>
<th>3am</th>
<th>4am</th>
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<th>6am</th>
<th>7am</th>
<th>8am</th>
<th>9am</th>
<th>10am</th>
<th>11am</th>
</tr>
</thead>
</table>

Please rate from 1 to 10, how you felt in the hour after waking: Physically? [9] Emotionally? [9]
Handout 5: Development of a Daily Routine

The aim of this part of the treatment process is to begin to get you back into more of a routine. At one level, we are doing this because your biological clock has difficulty in regulating your circadian system if you have an irregular pattern to your days. This is especially so if you don’t go outside much and are not exposed to bright light through the day. So, if your clock is compromised, adopting a routine in terms of sleep, activity, eating and relaxing will help to resynchronise your system. More directly, however:

- Regular bed and rising times promote healthy sleep that should prepare you better to face the challenges of the day, as well as reducing your levels of fatigue and boosting your immune system.

- Regular meal times allows your digestive system to prepare for the intake of food which leads to more efficient digestion. You thus gain greater nutritive value from your food, and the chances of gastric disturbances etc are greatly reduced.

- Regular exercise times also mean your body is more prepared to work and gain greater benefits from the activity. The negative effects of exercise are reduced by its regular performance at a time of day that you feel most able to cope with it.

- For the same reasons, regular relaxation times will make it easier to relax. We suggest these are set up for a few hours before bed-time to assist your body in the wind-down process.

Remember that ‘regular’ doesn’t mean ‘rigid’. You don’t have to do the same thing at the exact same time every single day. ‘Regular’ in the sense we mean it here simply means that on most days you tend to have a basic routine which you go through.

Here are some things to consider when setting up your routine:

1. Sleep-Wake times

On average, humans need between 7-8 hours sleep per night. There is no evidence that people with CFS actually need more sleep than healthy people (especially if it’s healthy sleep). Probably the best indicator as to how long you need to sleep each night is how long you slept before you were ill. So, if you were a seven hour a night person prior to contracting CFS, then seven hours per night is probably what you should aim for now. If you have been sleeping significantly longer than you used to, or is your sleep is very disturbed, you might need to decrease the number of hours you spend in bed gradually.

The other important thing to know is that spending longer than necessary in bed actually has a negative effect on the quality of your sleep. Instead of sleeping for longer, you are actually likely to have poorer quality, more shallow sleep. It has been shown that if you are a seven hour per night sleeper, but stay in bed for 9 hours,
cutting down the amount of time you spend in bed most often will lead to longer, higher quality sleep, even though you are in bed for less time. This is because you are likely to fall asleep faster, wake less often. So it is important to try to cut down the time you spend in bed if you are not sleeping.

2. Meal times:
Research suggests that our digestive system tends to work better if we have three reasonably evenly spaced meals through the day. About 4 or 5 hours between meals is normal, but you’ll need to factor in what’s simplest, given your daily life and the people you live with. An idea is to set up three meal-time windows throughout the day, each of about an hour (e.g. breakfast between 8:30-9:30, lunch 1-2pm and dinner between 6 and 7). You don’t have to be obsessive about when you eat, but you should aim to have regular eating patterns that you follow most days.

3. Exercise:
The main rule to follow in setting an exercise period is to time it for when you are normally feeling most able to deal with physical activity. Aim to carry out some kind of exercise at about the same time every day. The nature and intensity of the exercise has to be carefully thought out and must begin light and increase gradually. While it may be true that some CFS sufferers need to avoid physical exercise for a time, there is a lot of evidence that exercise is beneficial to many who have the illness, as long as it is conducted in consultation with a qualified health professional familiar with CFS. At this stage, just think about a time to engage in regular physical activity. What kind of exercise and how much you do is best worked out in therapy sessions.

4. Relaxing
We suggest that, at first at least, you give relaxation a try in the early to mid evening. This will help you to wind down towards healthy sleep. By relaxation, we mean an active practice, such as meditation, progressive muscle relaxation or breathing exercises. You may already have a particular type of practice that you like, if not, we can help you.
Your Goal Routine

You might like to set out your goal routine something like it has been below. In deciding on the times you set for your meals, sleep etc, you could look back at your sleep-activity diary and see if there are times you tend to do things already. If they're appropriate, it may be just a case of reinforcing these, rather than making any big changes.

Remember that your routine is a goal, and it may take some time to get into. Also remember that you don’t have to feel locked into it every day.

Bed time window       11-11:30pm
Rising time window    8-8:30am
Breakfast window      8-9am
Lunch window          1-2pm
Exercise window       2-3pm
Dinner Window         6-7pm
Relaxation window     9-10pm

Bring in your proposed routine next session, and we will work it through.
Handout 6: Light Box Prescription

As I have discussed with you, the temperature monitoring procedure suggests that one hour per day of exposure to the light-box between _____ and _____ every day for the next week is most appropriate. You should use the light as we have discussed in the sessions. You should place the light on a table in front of you, no more than 60cms from your face. This distance is important because even small increases in the distances will mean that the amount of light you receive will be dramatically reduced.

- A white table-cloth, or white paper on the table between you and the light will help by reflecting more light towards you.

- You do not need to look directly at the light. As long as your face is pointed towards it, you can eat or read in front of it, looking up for a second or two at it from time to time (say, every minute or so).

- If you suffer any discomfort in relation to the light, such as headaches, eye soreness or blurred vision, or you simply find the intensity too strong, stop the exposure sessions immediately and contact the CFS Clinic at Deakin (9251 7234).
Handout 7: Some Tips for Healthy Sleep.

Below are some basic factors that can improve the quality of your sleep dramatically.

- Go to bed only when you are sleepy
- Set your alarm to wake up at the same time everyday
- Try to avoid naps through the day
- Practice a relaxation technique before going to bed
- Reduce or eliminate caffeine, cigarettes and alcohol, especially in the evening.
- If you wake often at night to go to the toilet, try not drinking as much fluid in the hours before bed-time.
- Go to bed neither hungry nor full.
- Try to be more active through the day.
- Improve your sleeping environment (bed, darkness, quietness, temperature etc.)
- Develop a set of routines before bed to help you to wind down
- Work on thinking/worrying less when you are supposed to be sleeping
**Handout 8: Monitoring and Challenging Your Negative Thoughts**

Use this sheet to note when your negative thoughts occur and what they are. In the last column, provide a more realistic alternative.

<table>
<thead>
<tr>
<th>Time</th>
<th>Situation</th>
<th>Negative thought</th>
<th>Alternative</th>
</tr>
</thead>
<tbody>
<tr>
<td>9:30am, Fri</td>
<td>In bed, still tired after 10 hours sleep</td>
<td>I'll never get through the day</td>
<td>Oh well, at least I can rest later if I have to, and maybe I'll feel ok once when I'm up and about</td>
</tr>
</tbody>
</table>
APPENDIX F:

SLEEP LOG
Sleep-log Instructions:

The purpose of this log is to keep track of your sleep-wake patterns throughout treatment. Use a vertical line to indicate when you went to bed, and when you got out of bed in the morning. Then, simply fill in the time-lines to indicate the times you have slept, as with the sleep-activity log you filled in for the first two weeks of the study.

Sleep quality rating:

Rate how well you felt you slept out of 10 each morning in the box provided. Rate from 1 to 10, with a ‘1’ indicating that you slept extremely poorly, and a ‘10’ indicating that you slept extremely well.

Waking naturally vs waking via an alarm:

If you use an alarm clock or some other external prompt to wake you in the morning, indicate this by ticking the appropriate box over the sleep line. Many people set their alarm clocks but wake just before they go off anyway, and when this happens, you should tick the ‘Woke naturally’ box.

Physical and emotional wellness ratings:

Before you go to bed each night, you are asked to rate how you have been feeling physically and emotionally over the whole day. Use a scale from 1 to 10 to make these ratings, with ‘1’ indicating that you have felt extremely unwell, and a ‘10’ indicating that you have felt extremely well. Rate yourself compared to how you felt before you became ill. A ‘10’, for instance, would mean that you felt as well as an average healthy person when they are feeling at their best.
Figure F.1 Example of one participant's completed sleep log for two weeks.